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ARTICLE TYPE

Synthesis of Functionalized Dispiro-oxindoles through Azomethine Ylide Dimerization and Mechanistic Studies to Explain the Diastereoslectivity

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We have developed a one-pot synthesis of polycyclic fused dispiro-oxindole derivatives by the [3+3]-cycloaddition (dimerization) of azomethine ylide derived from condensation of isatin and proline. Dispiro-oxindole ring system is found at the core of a number of alkaloids, which possess significant biological activity and are interesting, challenging targets for chemical synthesis. We have demonstrated formation of two isomers, *cis* and *trans* with variable selectivity depending upon the substitutions pattern at N-atom of isatin moiety arises during this type of dimerization. We could also correlate these diastreoslectivity with DFT calculation. The formation and X-ray crystal structure of the *cis* isomer in this cycloaddition reaction is reported first time in the literature. We also gave clear insight of the mechanism of this dimerization reaction.

Introduction

The 1, 3-dipolar cycloaddition reactions is one of the versatile synthetic strategies for the construction of five,[1,2,3,4] and six-member ring heterocycles[5]. The routine [3+2]-cycloadditions of Azomethine ylide (AMY) are reported with variety of dipolarophiles e.g. alkene,[6,7,8,9,10] alkyne[11], carbonyl compound like aldehyde[12], anhydride[13], imine[14] etc. and limited [3+3]-cycloaddition are also known to synthesize piperazine derivatives by self condensation of AMY.[15] Highly functionalized piperazine moieties constitute the main structural element of different alkaloids[17] and pharmacologically active compounds. Piperazine ring structures have also importance in carbohydrate chemistry[18], drugs like anthelmintics[19], veterinary medicine to treat parasitic infectionsA[20].

Synthesis of piperazine derivatives are known in the literature employing several methods including [3+3]-cycloaddition reaction[21]. Among the varieties methods reported for AMY generations, one of the common methods for generation of AMY is condensation of isatin and proline. The molecules synthesized by this type of AMY, for a long time, have pharmacological as well as biological importence.[22] Perumal et al. have reported[15b] such dimer (I) for very good activity towards anti-tuberculosis; however they couldn't predict the right structure of the dimer (Fig.-1). Recently, Essassi et al reported[23] the correct structure of the dimer (II) by single crystal X-ray crystallography (Fig.-1). Tuberculosis (TB), caused by Mycobacterium tuberculosis (M. Tb), is a major infectious disease suffered by mankind in mostly low and middle income countries, although no region in the world remains untouched. According to World Health Organization (WHO) data, every second a newly infection by tuberculosis bacillus occurs somewhere in the world; the number of infections is constantly rising and will soon affect a third of the world's population. The statistics indicate that 1.3 million people throughout the world died from TB in 2008.[16a] Presently our group is involved in developing anti-tuberculosis drug candidates. Our research interest[1d,24] in AMY cycloaddition and other project involving these type of isatin derived AMY gave surprisingly the dimers. We want to report in this present article the systematic studies involving the effect of EWG, EDG, and Lewis Acid on the [3+3]-cycloaddition reaction of AMY generating from isatin and proline. Biological testing of all these compounds towards anti-tuberculosis activities will give very important information and may lead to a very good hit compound for the above mentioned purpose.

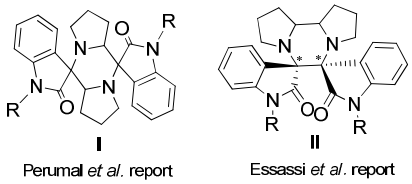
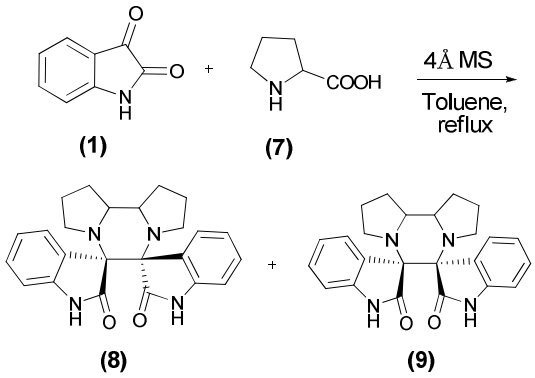


Figure-1: Two previously reported structures of the dimer.

Results and Discussion

The AMY derived from condensation of isatin (**1**) and proline (**7**) is found to be very reactive towards [3+2]-cycloaddition with electron deficient dipolarophiles.[16,25] Our observation is interesting for the similar reaction without any dipolarophile. **1** and **7** when admixed together in presence of 4Å molecular sieves in toluene, under refluxing condition, **1** was completely consumed within four hour. After complete analysis of the above mentioned reaction, gave two products **8** and **9** in (1.3 : 1) diastereomeric ratio (Scheme-1). In ^{1}H NMR of **8**, four aromatic



Scheme 1. Dimerization of AMY.

protons were appeared which indicates this molecule had isatin moiety. Interestingly, compound **9** showed much deferent ^{1}H NMR. In aromatic region of compound **9**, eight protons were observed followed by twice number of protons in aliphatic region as compared to **8**. These observations indicated that the presence of two proline moieties i.e. a molecular symmetry could be present in compound **8**. The mass spectrum of both the compounds **8**, and **9** gave the same molecular ion peak (m/z).

Fortunately, both compounds **8, 9** were crystalline solid at room temperature. The Single crystal X-ray data analysis of both compounds revealed *trans* dimer **(8)** and another was *cis* dimer **(9)** of AMY (fig-2). Both compounds were diastereomers with respect to each other and in **8** half of the total protons of molecule were magnetically equivalent while in **9** all protons were magnetically non equivalent due to different chemical environment. In this fashion the occurence of the *cis* isomer during this type dimerization reaction was doccumented first time in the literature.

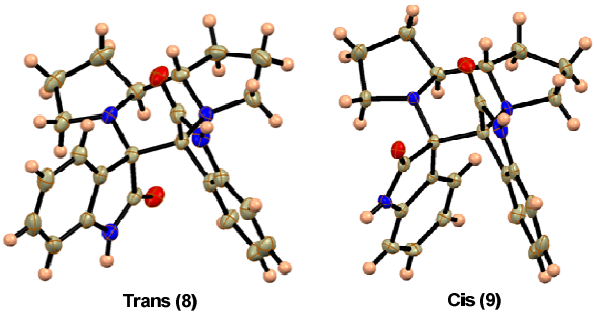
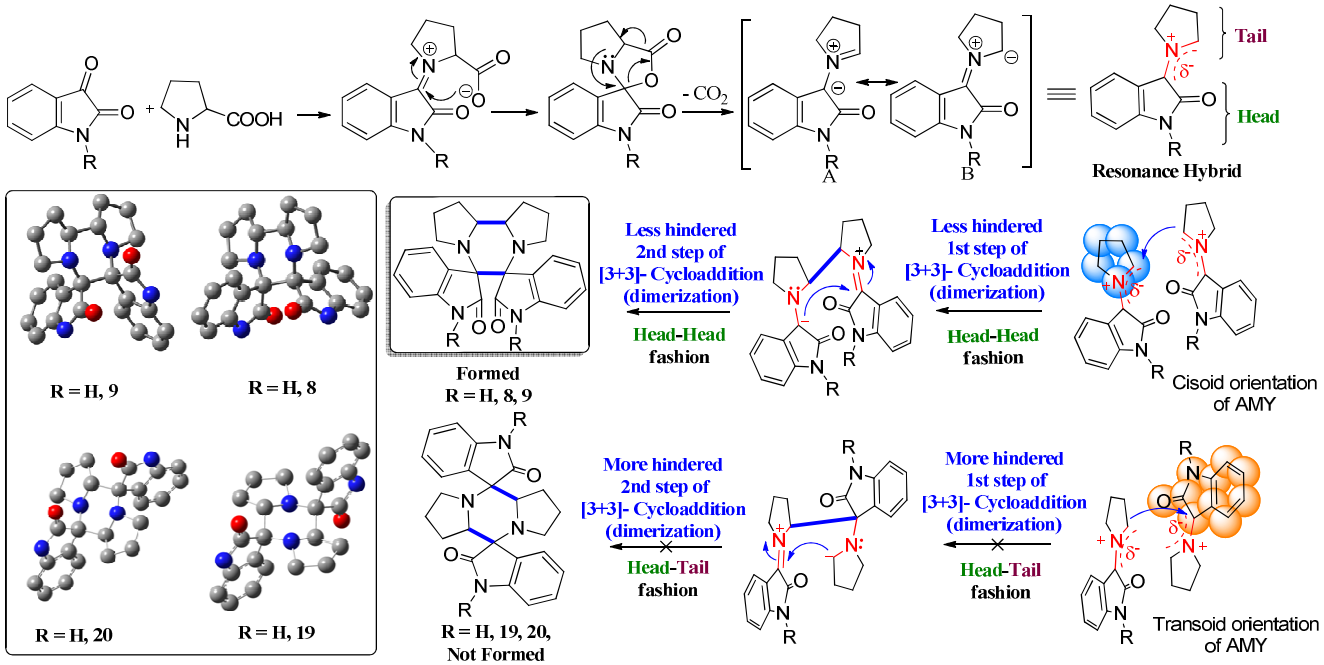


Figure 2. ORTEP Diagram of the molecular structure of **8** and **9**.

The possible mechanism for the dimerization of AMY is reported in literature.[26] Two kinds of dimerizations of AMY generated in the above mentioned manner are possible, either head-head fashion of the resonance hydrid or by head-tail manner of the same resonance hybrid (Scheme-2). Interestingly, the product observed is only of former type. The less hindered head-head 1st step of the dimerization may be driving force for forming **8** instead of **19**. DFT calculation was performed to critically examine this dimerization motive.

When **8** was refluxed in toluene with 4Å MS under N_2 atmosphere, **9** formed slowly and the conversion was observed in (50: 50) ratio after 48 h. Again similar observation was noticed with **9** (Scheme-3). This is only possible when the activation energy for the both products is very close and passes through a common intermediate.

The lock and key chemistry of this type of AMY dimerization was also studied by taking different electron donating and electron withdrawing substituent at N- atom of isatin. When N-methyl isatin **(2)** was refluxed with **7** same result (**10**, **11**) was obtained



Scheme 2. Proposed mechanism of AMY generation and its dimerization.

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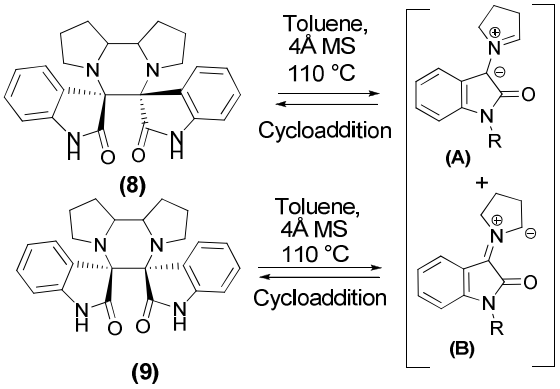
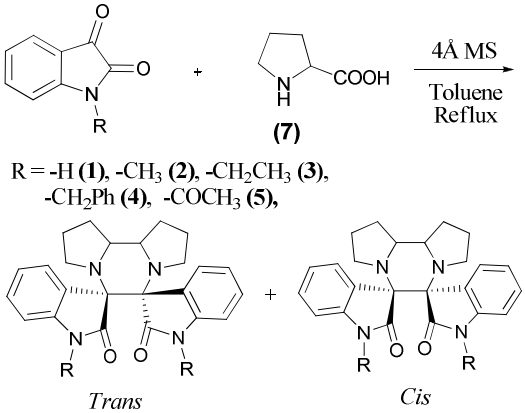


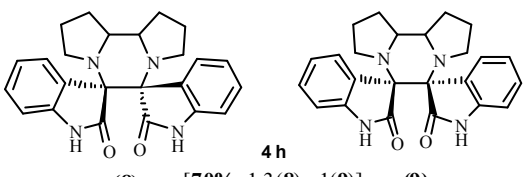
Scheme 3. Interconversion of *trans* and *cis* dimers

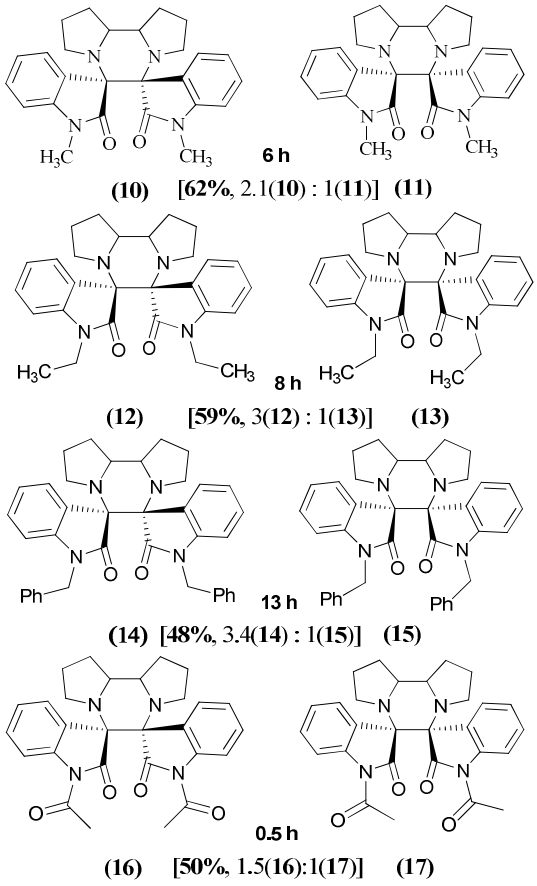
as in above mentioned reaction. The rate of reaction is, somewhat, slower than the isatin reaction (table-1) and *trans*-isomer was formed as major. N-Ethyl isatin **(3)** derived AMY underwent cycloaddition reaction in same condition and gave both isomers **(12, 13)** in moderate yield. This reaction was slower than N-methyl isatin **(2)** case and completed in 8 h. The *trans* diastereomer **(12)** was found to be major and formed first relative to *cis* diastereomer **(13)** (table-1).

The effect of benzyl group on the dimerization of AMY derived from N-Benzyl isatin (**4**) was also studied. This reaction was very slow in compare to other derivatives of isatin studied by us, and completed in 13 h. In this dimerization reaction *trans* dimer (**14**) was formed as major

Table 1.[a,b] Dimerization of AMY with different substituent of isatin.



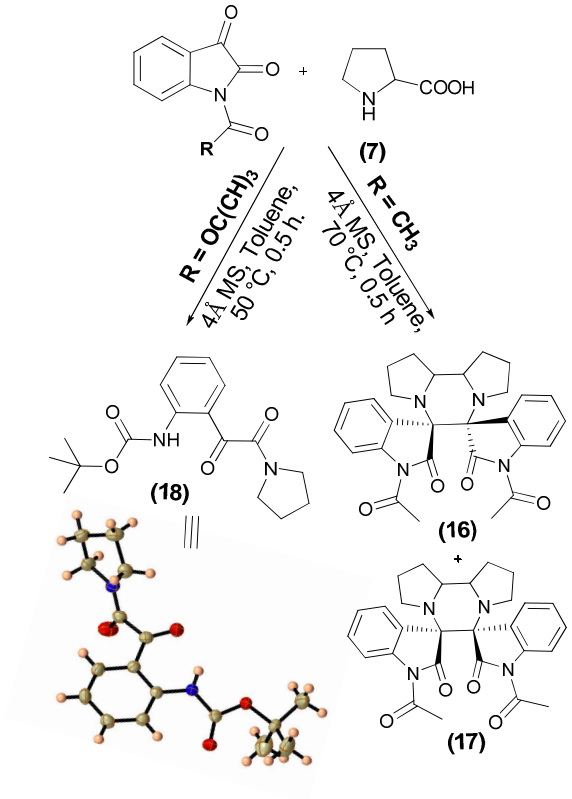




[a] Reactions were performed in toluene,[b] Isolated yield by flash column chromatography.

product in compare to *cis* dimer (**15**). The yield of **15** was very poor (table-1), this could be due to steric effect of benzyl groups that opposed the reaction between two AMY fragment in *cis* orientation. The result obtained by substituting hydrogen of NH in isatin with methyl, ethyl and benzyl was found that the yield of *cis* product was decreased in same trend as bulkiness of the group increases. So, it was cleared that size of substituent played major role for controlling the diastreoslectivity of AMY dimerization.

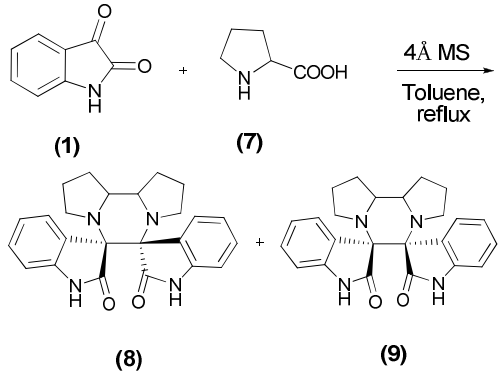
After studying the effect of electron donating and bulkier group on dimerization of AMY, the EWG like acetyl and Boc were taken as substituent for our investigation. When N-Acetyl isatin (**5**) was applied in the same reaction condition, it was observed that reaction was very fast and completed within 30 min. This reaction also gave the *trans* (**16**) and *cis* dimer (**17**) in quantitative yield. The ratio of *trans* and *cis* (1.5 : 1) was close to isatin ratio (table-1). In **16**, ^{1}H NMR pattern was slightly different from above mentioned analogue due to presence of the acetyl group.



Scheme 4. Effect of N-acetyl and N-Boc group on AMY dimerzation.

When N-Boc isatin (**6**) was refluxed with proline (**7**), reaction was completed within 0.5 h. Interestingly, after complete analysis of isolated product we found that in this case dimerization of AMY did not occur, in spite of this five member ring of isatin was opened with proline (**7**) to form carbamate derivatives (**18**). The carbamate derivative **18** was found to be crystalline solid and single crystal X-ray was taken. This observation is documented in the literature,[26] but our finding contradicts in the case of N-acetyl isatin where the dimerized product could only be isolated but it was reported to cleave as observed in N-Boc case. This could be due to special arrangement of oxygen of isatin carbonyl and Boc-ester moiety which brings proline closer to isatin carbamate functionality to cleave it selectively. This reaction also disclosed the stability and reactivity of isatin to form AMY depending upon the different substituent present at N- atom of isatin (Scheme 4).

Table 2. Screening of temperature *vs* solvent effect on isatin and Proline reaction.



Entry No.	Solvent	Temp. (°C)	Time(h)
1	Toluene	110	4
2	Methanol	64	1
3	Dioxane : Methanol (1:1)	70	1

When reaction was screened by changing the solvent, it was observed that in toluene reaction was completed within 4 h (Table-2). While reaction time was decreased in methanol and methanol: Dioxane (1:1) as solvent. This could be due to the solvent role in transition state stabilization. The TS of AMY formation in this reaction was polar (confirmed by DFT) and stabilized by the polar solvent.

Mechanistic Studies

The regio and diastreoslectivities of this type of AMY dimerization derived from isatin derivatives and proline (**7**) were also studied by us using *ab initio* density functional theory (DFT). All the structures have been geometry optimized using B3LYP functional employing 6-31G(d,p)[27,28] basis set as implemented in Gaussian-09 code.[29] Vibrational analysis has been performed for all the stationary points. Transition states are characterized by one negative imaginary frequency along the reaction coordinate. For all transition state structures, the intrinsic reaction coordinate (IRC)[30] calculation was performed to ascertain that each transition state connected the expected reactants and products.

Theoretical calculation for the 1,3-dipolar cycloaddition reaction of AMY generated by the above discussed manner from isatin is reported in the literatures.[31] However, our interest was to know the difference between activation energy (ΔE_a) of transition states among both diasteriomers (*cis, trans*). The activation energy (ΔE_a) for *cis* and *trans* diasterioisomeric products was analyzed.The activation energy for *trans* product **8** (4.2 kcal/mol) was found to be less than the *cis* product **9** (5.1 kcal/mol) (entry 1, 2, table 3). Due to this reason the transoid orientation of two

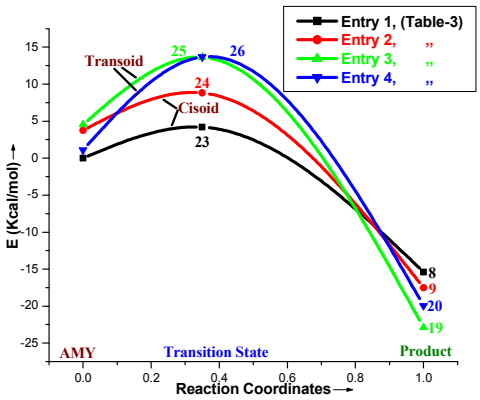


Figure 3: Energy profile diagram of [3 + 3] dimerization reaction of isatine – proline derived AMY.

AMY could surpass the energy barrier more frequently than the cisoid orientation. This DFT interpretated data could explain the regeochemistry and selectivity of the experimental result where product **8** was found to be major. The computed transition

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Table 3. Energetics of [3 + 3] – Cycloaddition (dimerization) reaction and their activation energy (R = **H**).
0.00 = -814811.5780101882 Kcal/mol.

S. No	R	E_R (2 AMY) (Kcal/Mol)	E_p (Kcal/Mol)	TS Frequency (cm^{-1})	E_{TS} (Kcal/Mol)	E_a Kcal/mol)
1.	Trans, H**(1),** (Experimental)	0.00	-15.375 **(8)**	-273.52	4.200 **(23)**	4.2
2.	Cis, H**(1)** (Experimental)	3.75	-17.5125 **(9)**	-286.04	8.813 **(24)**	5.1
3.	Trans, H**(1)** (Expected)	4.53	-22.890 **(19)**	-290.61	13.64 **(25)**	9.1
4.	Cis, H**(1)** (Expected)	1.10	-19.943 **(20)**	-231.59	13.674 **(26)**	12.6

Table 4. Energetics of [3 + 3] – Cycloaddition (dimerization) reaction and their activation energy (R = **Benzyl**).
0.00 = -1154134.9684358091 Kcal/mol.

S. No	R (Experimental)	E_R (2 AMY) (Kcal/Mol)	E_p (Kcal/Mol)	TS Frequency (cm^{-1})	E_{TS} (Kcal/Mol)	E_a Kcal/mol)
5.	Trans, Bn **(4)**	0.00	-13.577 **(14)**	-277.69	5.000 **(27)**	5.0
6.	Cis, Bn **(4)**	2.19	-17.467 **(15)**	-295.43	7.725 **(28)**	7.8

E_R = Energy of Reactants, E_p= Energy of Products, E_{TS} = Energy of Transition States, **Ea** = Activation energy.

state structures were found to be polar with high dipole moment (*trans,* **8**: μ=1.7 D; *cis,* **9**: μ=3.8 D). The high dipole moment may have resulted the higher stability of TS in polar solvents compared to non polar solvents. This prediction also support our experimental results where the reaction is found to be faster in polar solvent (entry 3, table-2). Similarly, for N-Benzyl substituted AMY dimerization, activation energy of *trans* adduct (**14**) is (5.0 kcal/mol) lesser than *cis* adduct, **15** (7.8 kcal/mol) due to which the experimental yield of *trans* adduct was found to be higher than *cis* adduct (**15**) (entry 5, 6, table 4). It was also noticed that the activation energy difference between **8** and **9** (0.8 kcal/mol) was less than **14** and **15** (2.8 kcal/mol) (fig. 3, 4). This activation energy difference between differently substituted adducts resulted in variation in the ratio of their corresponding diastereoslectivity. Steric hindrance have also played a major role with respect to stereo selectivity as well as reaction productivity.

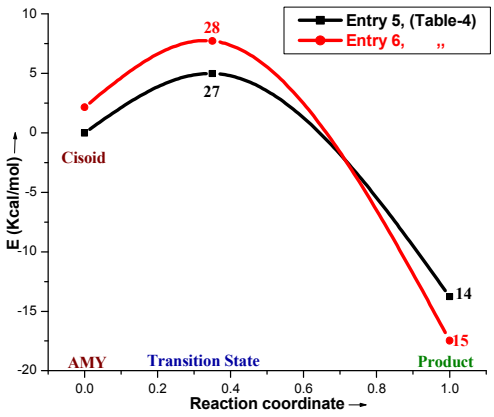

Figure 4: Energy profile diagram of [3 + 3] dimerization reaction of N - Benzyl isatine – proline derived AMY.

The reason behind the non-existence of other expected adducts (**19**, **20**) during experiment, could be explained with the help of DFT studies. The activation energy for both **19** (9.1 kcal/mol) and **20** (12.6 kcal/mol) isomers were more than the experimentally observed adducts (entry 3, 4, table 3, fig- 3). This energy difference between transition states may be responsible for the formation of **8** and **9** in spite of **19** and **20**.

Conclusions

In conclusion, dimerization of AMY was well affected using different substituent at N-atom of isatin and also it was evidented that presence of EWG like Boc banned the AMY formation from isatin and proline. DFT studies supported the experimental results and gave conclusive evidence of activation energy differences of TSs. X- Ray crystallography provided complete structure of both isomers of dispiro-oxindoles. The formation of the *cis* compound, which was otherwise neglected as polar impurities in earlier studies, was characterized fully first time in the literature. Bioactivity of the newly synthesized compounds will be published elsewhere.

Experimental

General:

The reagents isatin **(1)**, proline **(7)** were commercially available and were used without further purification. Toluene was dried over P_2O_5 then sodium metal and stored at 4Å molecular sieves for at least 48 hr. prior to use. N- Methyl,[32] N-Ethyl,[32] N-Benzyl,[32] N- Acetyl[33] and N- Boc Isatin[34] were synthesized according to their reported procedure. Reactions were performed under N_2 in oven dried glassware. The developed chromatogram was analyzed by UV lamp (254 nm), or iodine stain. Products were purified by flash chromatography on silica gel (mesh size 230-400) and further purified by crystallization with ethanol at r.t. Chemical shifts of Proton and ^{13}C NMR spectra are expressed in parts per million (ppm). All coupling constants are absolute values and are expressed in Hz. The description of the signals include: s = singlet, brs = broad singlet d = doublet, dd = double

doublet, t = triplet, q = quartet, m = multiplet and td = triplet of doublet.

Typical experimental procedure for alkylation of Isatine (Procedure A):

A round bottom flask was charged with isatin, K_2CO_3 and dry acetonitrile followed by addition of alkyl iodide under nitrogen atmosphere. Resulting mixture was refluxed overnight and reaction progress was monitored by TLC. After completion of the reaction, solvent was evaporated at reduced pressure and crude mixture was quenched by water. Ethyl acetate was added to the resulting mixture and aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over Na_2SO_4, concentrated *in vaccuo*. and purified by flash column chromatography with (EtOAc/Hexane) to afford desire alkylated product.

Synthesis of 1-methylindoline-2,3-dione (2): Prepared by following procedure A; isatin (1 g, 6.8 mmol), methyl iodide (1.16 g, 8.16mmol), K_2CO_3 (2.81 g, 20.4 mmol) and dry acetonitrile (30 ml), yield (0.82g, 75 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.63 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.13 (td, J = 7.6 Hz, J = 1.3 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H),3.25 (s, 3H).

Synthesis of 1-ethylindoline-2,3-dione (3): Prepared by following procedure A; isatin (1 g, 6.98 mmol), ethyl iodide (1.3 g, 8.38mmol), K_2CO_3 (2.81 g, 20.4 mmol), dry acetonitrile (30 ml), yield (0.88 g, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (m, 2 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 7.6 Hz, 1 H), 3.76 (q, *J* = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H).

Synthesis of 1-benzylindoline-2,3-dione (4): Prepared following procedure A; isatin (1 g, 6.98 mmol) in dry acetonitrile (30 ml), benzyl iodide (1.16 g, 8.16 mmol) and K_2CO_3 (2.81 g, 20.4 mmol) yield (1.12 g, 68 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.6 Hz, 1H), 7.4 (td, J = 7.6, 2.9 Hz, 1H), 7.2 – 7.3 (m, 5H), 7.01(t, J = 7.6 Hz, 1H), 6.7 (d, J = 7.6 Hz, 1H), 4.85 (s, 2H).

Synthesis of 1-acetylindoline-2,3-dione (5): Isatin (1 g, 6.98mmol) and acetic anhydride (16 ml) was heated at 90 – 100°C under nitrogen atmosphere for overnight. Reaction was monitored by TLC and after complete consumption of isatine, mixture was allowed to cool at rt. The crude mixture was kept in freeze for overnight to get fine yellow crystal of the product (0.82 g, 62%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.44 (d, J = 7.9 Hz, 1H), 7.8 (dd, = 7.43, 1.4 Hz, 1H), 7.74 (td, J = 7.9, 1.4 Hz, 1H), 7.35 (td, J = 7.9, 1.4 Hz, 1H), 2.75 (s, 3H).

Synthesis of tert-butyl 2,3-dioxoindoline-1-carboxylate (6):

To a solution of DMAP (0.042 mg, 0.5 mmol) in dry THF (32 ml), isatin (1 g, 6.8 mmol) was added at room temperature. Then di-*tert*-butyl dicarbonate (1.77 g, 1.2 mmol) was slowly added to the mixture. After stirring for 6 h, water (20 ml) was introduced to precipitate the product. After filtration, the product was recrystallized with DCM/Hexane. The resultant solid was dried in vacuo to give 1-tert-butoxycarbonyl isatine as (1 g, 60%). %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.8 Hz, 1H), 7.72 (m, 2H), 7.29 (d, J = 7.8, 1H), 1.65 (s, 9H).

Typical experimental procedure for cycloaddition reaction of AzomethineYlied (Procedure B):

The round bottom flask was charged with N-substituted isatine derivative, proline and 4 Å MS followed by successive addition of dry toluene under nitrogen atmosphere. Reaction mixture was brought to reflux and was monitored by TLC at different interval. After completion of reaction, mixture was cooled at r.t., filtered through celite and evaporated *in vacuo*. The crude mixture was purified by flash column chromatography with EtOAc/Hexane and recrystallized with ethanol to afford heptacyclic adduct.

(**8, 9**) Reaction was performed by following procedure B; isatin (0.5 g, 3.4 mmol), proline (0.391 g, 3.4 mmol), toluene (30 ml), 4Å MS (200 mol%), time = 4 h.

Synthesis of (3R,7'S) -1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6]dodecane-7',3"-indole]-2,2"-dione (8):

Yield = 40%, white solid, **mp** = 188 - 190 °C (Decomposed) melted at 285 - 290 °C, **IR** (neat) ν_{max} 3303, 3176, 3153, 3082, 2973, 2948, 2848, 2810, 1724, 1701, 1619, 1471, 1187, 767, 683 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (d, J = 7.6 Hz, 2H), 7.2 – 7.3 (brs, 2H), 7.05 (td, J = 7.6, 1.1 Hz, 2H), 6.9 (td, J = 7.6, 1.1 Hz, 2H), 6.47 (d, J = 7.7 Hz, 2H), 3.62 (m, 2H), 2.62 (td, J = 8.7, 2.4 Hz, 2H), 2.17 (q, J = 8.5 Hz, 2H), 1.9 (m, 2H), 1.78 (m, 2H), 1.62 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$ and DMSO - D_6): δ 20.5, 27.1, 47.1, 58.7, 68.1, 108.7, 120.9, 125.8, 126.1, 128.5, 141.6, 175.9. TOF MS ES+401 (M+ H). HRMS calcd. for $C_{24}H_{24}N_4O_2$ (M+H) 401.1977 found 401.1987.

Synthesisof (3R,7'R) -1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6]dodecane-7',3"-indole]-2,2"-dione (9): Yield = 30%,white solid, **mp** = 198 - 200 °C (Decomposed) melted at 285 - 290 °C, **IR**neat): ν_{max} 3280, 3195, 3083, 2965, 2820, 1713, 1617, 1469, 1192, 754. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, 7.7 Hz, 1H), 7.5 – 7.63 (brs, 2H), 7.28 (t, J = 7.7 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 6.47 (t, J = 7.7 Hz, 1H), 6.08 (d, J = 7.7 Hz, 1H), 3.88 (td, J = 10.1, 5.8 Hz, 1H), 3.72 (td, J = 10.1, 5.8 Hz, 1H), 2.87 (m, 2H), 2.56 (td, J = 8.7, 2.7, 1H), 2.17 (q, J = 8.7 Hz, 1H), 1.92 (m, 2H), 1.85 (m, 1H), 1.77 (m, 2H), 1.68 (m, 2H), 1.52 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$ and DMSO - D_6): δ 20.3, 20.4, 26.8, 27.0, 45.7, 46.1, 58.0, 59.8, 66.9, 70.5, 108.3, 108.8, 119.5, 119.8, 124.6, 125.4, 125.7, 128.1, 128.3, 128.5, 142.3, 142.6, 173.8, 174.4, TOF MS ES+401 (M+ H). HRMS calcd. for $C_{24}H_{24}N_4O_2$ (M+H) 401.1977 found 401.1976.

(**10, 11**) Reaction was performed by following procedure B; N-methyl isatin (0.5 g, 3.105 mmol), proline (0.357 g, 3.105 mmol), dry toluene (30 ml), 4Å MS (200 mol%), time = 6 h.

Synthesis of (3R,7'S)-1,1"-dimethyl-1,1",2,2" tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (10):

Yield = 42 %,white solid, **mp** = 183 - 186 °C, **IR** (neat): ν_{max}

2970, 2816, 2313, 1737, 1696, 1608, 1466, 1344 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, J = 7.7 Hz, 2H), 7.08 (t, J = 7.7 Hz, 2H), 6.89 (t, J = 7.7 Hz, 2H), 6.38 (d, J = 7.7 Hz, 2H), 3.72 (t, J = 4.7 Hz, 2H), 2.9 (s, 6H), 2.62 (td, J = 8.2, 2.4 Hz, 2H), 2.09 (q, J = 8.2 Hz, 2H), 1.9 (br s, 2H), 1.79 (q, J = 8.6 Hz, 2H), 1.63 (br m, 4H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 24.9, 27.6, 47.8, 59.3, 69.0, 107.2, 121.6, 125.2, 125.7, 129.1, 143.6, 174.7. TOF MS ES+ 429 (M+H). HRMS calcd. for $C_{26}H_{29}N_4O_2$ (M+H) 429.229 found 429.2301.

Synthesisof (3R,7'R)1,1"-dimethyl-1,1",2,2"tetrahydrodispiro [indole-3.8' [6,9]diazatricyclo[7.3.0.02,6]dodecane-7',3"-indole]-2,2"-dione (11):

Yield = 0.265 g, 20 %,white solid, **mp** = 174 - 176 °C, **IR** (neat): ν_{max}3016, 2971, 2316, 1736, 1368, 1222 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (d, J = 7.7 Hz, 1H), 7.3 (t, J = 7.7 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 7.03 (t, J = 7.7 Hz, 1H), 6.6 (dd, J = 4.6, 3.1 Hz, 2H), 6.43 (t, J = 7.7 Hz,1H), 6.04 (d, J = 7.7 Hz, 1H), 3.97 (td, J = 5.8, 4.3 Hz, 1H), 3.16 (s, 3H), 2.87 (m, 1H), 2.87 (m, 1H), 2.83 (s, 3H), 2.73 (br d, J = 7.4 Hz, 1H), 2.53 (td, J = 7.3, 2.7 Hz, 1H), 2.08 (q, J = 8.6 Hz, 1H), 1.92 (m, 2H), 1.82 (m, 1H), 1.71 (dd, J = 7.8, 2.75 Hz, 1H), 1.65 (m, 2H), 1.5 (td, J = 7.7, 2.7 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9, 21.1, 25.6, 26.1, 27.4, 27.8, 46.6, 46.9, 58.9, 60.9, 67.8, 71.5, 107.3, 107.6, 120.7, 121.2, 124.8, 125.2, 125.8, 128.9, 129.0, 129.1, 144.6, 173.0, 174.0. TOF MS ES+429 (M+H). HRMS calcd. for $C_{26}H_{28}N_4O_2Na$ (M+Na) 451.21045 found 451.2120.

(**12, 13**) Reaction was performed by following procedure B; N-ethyl isatin (0.5g, 2.857 mmol), proline (0.328 g, 2.857mmol), dry toluene (30 ml), 4Å MS (200 mol%), time = 8 h.

Synthesis of (3R,7'S)-1,1"-diethyl-1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (12):

Yield = 44 %,white solid, mp = 180 - 181°C, **IR** (neat): ν_{max} 2969, 2810, 1696, 1606, 1465, 1347, 1205, 1133, 1094 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 (d, J = 7.7 Hz, 2H), 7.05 (t, J = 7.7 Hz, 2H), 6.83 (t, J = 7.7 Hz, 2H), 6.42 (d, J = 7.7 Hz, 2H), 3.66 (br t, J = 5.5, 4.9Hz, 2H), 3.4 (q, J = 7.1Hz, 2H), 3.5 (q, J = 7.2 Hz, 2H), 2.58 (td, J = 8.6, 2.2 Hz, 2H), 2.05 (q, J = 8.4 Hz, 2H), 1.87 (br m, 2H), 1.76 (m, 2H), 1.6 (m, 4H), 1.07 (t, J = 7.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.7, 20.9, 27.5, 33.9, 47.5, 59.2, 68.2, 107.4, 121.7, 126.0, 126.2, 129.0, 142.9, 174.1. TOF MS ES+ 457 (M+H). HRMS calcd. for $C_{28}H_{33}N_4O_2$ (M+H) 457.2603 found 457.2614.

Synthesisof (3R,7'R)-1,1"-diethyl-1,1",2,2"-tetrahydrodispiro[indole-3.8' [6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (13):

Yield = 15 %,white solid, **mp** = 180 - 181°C, **IR** (neat): ν_{max}2968, 2931, 2874, 2809, 1714, 1605, 1462, 1153, and 1221. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (d, J = 7.7 Hz, 1H), 7.29 (td, J = 7.7, 1.1 Hz, 1H), 7.6 (td, J = 7.7, 1.1 Hz, 1H), 7.01 (td, J = 7.7, 1.1 Hz, 1H), 6.6 (d, J = 7.7 Hz, 2H), 6.41 (td, J = 7.7, 1.1 Hz, 1H), 5.98 (d, J = 7.7 Hz, 1H), 3.98 (td, J = 10.2, 5.8, 4.2 Hz, 1H), 3.78 (q, J = 7.5 Hz, 1H), 3.69 (q, J = 7.5 Hz, 1H), 3.58 (q, J = 7.2 Hz, 1H), 3.24 (q, J = 7.2 Hz, 1H), 2.91 (td, J = 9.9, 5.9, 1H), 2.76 (td, J = 8.3, 2.2 Hz, 1H), 2.54 (td, J = 8.7, 2.7 Hz, 1H), 2.1 (q, J = 8.7 Hz, 1H), 1.92 (m, 2H), 1.81 (m, 1H), 1.7 (m, 4H), 1.5 (m, 2H), 1.24 (t, J = 7.3 Hz, 3H), 0.58 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 11.6, 12.6, 20.9, 21.1, 27.4, 27.8, 34.1, 34.2, 46.6, 46.8, 58.9, 60.9, 67.6, 71.3, 107.3, 107.6, 120.5, 120.9, 125.2, 125.4, 126.1, 128.8, 129.0, 129.3, 143.6, 143.7, 172.3, 173.4. TOF MS ES+ 457 (M+ H). HRMS calcd. for $C_{28}H_{32}N_4O_2Na$ (M+Na) 479.2418 found 479.2439.

(**14, 15**) Reaction was performed by following procedure B; N-benzyl isatin (0.5 g, 2.11mmol), proline (0.243 g, 2.11 mmol), dry toluene (30 ml), 4Å MS (200 mol%), time = 13 h.

Synthesis of (3R,7'S)-1,1"-dibenzyl-1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (14):

Yield = 37%, white solid, **mp** = 172 - 173 °C, **IR** (neat): ν_{max}2975, 2949, 2878, 2812, 1693, 1604, 1468, 1339, 1180, 1165, 767cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.3 (d, J = 7.7 Hz, 2H), 7.2 – 7.25 (m, 6H), 7.11 (t, J = 7.7 Hz, 2H), 6.95 (t, J = 7.7 Hz, 2H), 6.7 (t, J = 7.7 Hz, 2H), 6.31 (d, J = 7.7 Hz, 2H), 4.88 (d, J = 15.7 Hz, 2H), 4.47 (d, J = 15.7 Hz, 2H), 3.7 (t, J = 6.7 Hz, 2H), 2.6 (t, J = 6.7 Hz, 2H), 2.13 (q, J = 6.7 Hz, 2H), 1.91 (br, 2H), 1.78 (dd, J = 8.3, 7.8 Hz, 2H), 1.65 (m, 4H), 1.23 (td, J = 7.0, 0.78 Hz, 2H).**^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.0, 27.5, 43.3, 47.7, 59.4, 68.6, 108.5, 122.1, 125.8, 126.0, 127.45, 127.6, 128.7, 128.9, 135.8, 143.1, 174.6. TOF MS ES+581 (M+ H). HRMS calcd. for $C_{38}H_{37}N_4O_2$ (M+H) 581.2916 found 581.2933.

Synthesisof (3R,7'R)-1,1"-dibenzyl-1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (15):

Yield = 11 %,white solid, **mp** = 175 - 176 °C, **IR** (neat): ν_{max} 2984, 2949, 2828, 2352, 2312, 1708, 1606, 1485, 1464, 1365, 1349, 1166, 745, 741, 696 cm^{-1}.**^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.1(d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.7, 2H), 7.23 – 7.16 (br m, 4H), 7.1 – 7.04 (m, 2H), 7.03 – 6.95 (m, 3H), 6.49 – 6.43 (dd, J = 7.7, 1.8 Hz, 3H), 6.42 – 6.38 (d, J = 7.7 Hz, 2H), 6.15 (d, J = 7.7 Hz, 1H), 5.1 (d, J = 15.9 Hz, 2H), 4.8 (d, J = 15.9 Hz, 1H), 4.34 (d, J = 15.9 Hz, 1H), 4.04 (td, J = 9.9, 5.8 Hz, 1H), 2.95 (td, J = 9.9, 5.8 Hz, 1H), 2.85 (td, J = 8.4, 2.4 Hz, 1H), 2.61 (td, J = 8.4, 2.4 Hz, 1H), 2.21 (q, J = 8.7 Hz, 1H), 1.98 (m, 2H), 1.86 (m, 1H), 1.74 (m, 4H), 1.54 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.9, 21.1, 27.5, 27.8, 43.4, 43.9, 46.6, 47.0, 59.1, 60.9, 67.7, 71.3, 108.9, 109.0, 121.1, 121.3, 124.7, 125.3, 126.2, 126.4, 126.9, 127.2, 127.5, 128.6, 128.7, 128.9, 129.1, 129.2, 135.1, 136.5, 143.6, 144.1, 173.1, 173.9. TOF MS ES+581 (M+ H).HRMS calcd. for $C_{38}H_{37}N_4O_2$ (M+H) 581.2916 found 581.2933.

(**16**, **17**) Reaction was performed by following procedure B; N-acetyl isatin (0.1g, 0.5291mmol), proline (0.06 g, 0.5291mmol), dry toluene (4ml), 4Å MS (200 mol%), time = 30 min.

Synthesis of (3R,7'S)-1,1"-diacetyl-1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (16):

Yield = 30 %, white solid, **mp** = 170 °C (Decomposed) melted at 240 - 250°C. **IR** (neat): ν_{max} 2961, 2917, 2866, 2815, 1750, 1708,

1461, 1331, 1268, 1152, 1011, 761 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.18 (td, J = 7.8, 1.4 Hz, 2H), 7.07 (td, J = 7.8, 1.4 Hz, 2H), 3.64 (m, 2H), 2.28 (m, 2H), 2.62 (s, 6H), 2.10 (q, J = 8.3 Hz, 2H), 1.98 (m, 2H), 1.82 (m, 2H), 1.69 (m, 2H), 1.61 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.1, 26.9, 27.8, 48.1, 59.6, 69.3, 116.4, 124.4, 124.6, 124.6, 130.4, 140.0, 169.9, 175.5. TOF MS ES+ 485 (M+ H). HRMS calcd. for $C_{28}H_{28}N_4O_4Na$ (M+Na) 507.2008 found 507.2004.

Synthesis of (3R,7'R)-1,1"-diacetyl-1,1",2,2"-tetrahydrodispiro[indole-3.8'-[6,9]diazatricyclo[7.3.0.02,6] dodecane-7',3"-indole]-2,2"-dione (17):

Yield = 20 %, white solid, **mp** = 170 °C (Decomposed) melted at 240 - 250°C. **IR** (neat): ν_{max} 2961, 2925, 2868, 2823, 1759, 1708, 1462, 1332, 1303, 1270, 1161, 760 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.33 (d, J = 7.9 Hz, 1H), 8.23 (m, 2H), 7.61 (dd, J = 7.9, 1.1 Hz, 1H), 7.43 (td, J = 7.9, 1.1 Hz, 1H), 7.37 (td, J = 7.9, 1.1 Hz, 1H), 7.3 (td, J = 7.9, 1.1 Hz, 2H), 4.19 (dd, J = 10.8, 6.2 Hz, 1H), 3.72 (d, J = 10.8, 6.2 Hz, 1H), 2.75 (s, 3H), 2.73 (3, 3H), 2.71 (m, 2H), 2.19 (q, 1H), 1.87 (q, 1H), 1.73 (m, 1H), 1.63 (m, 1H), 1.53 (m, 1H), 1.45 (m, 1H), 1.41 (m, 1H), 1.25 (m, 2H), 0.83 (m, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.8, 21.2, 23.7, 24.4, 27.1, 27.2, 46.0, 46.8, 60.7, 62.4, 67.1, 68.1, 116.3, 116.4, 123.9, 124.0, 125.2, 125.7, 127.4, 128.5, 129.5, 129.6, 139.7, 140.6, 170.7, 170.9, 176.4, 176.7. TOF MS ES+ 485 (M+ H).HRMS calcd. for $C_{28}H_{28}N_4O_4Na$ (M+Na) 507.2008 found 507.2020.

Synthesis of tert-butyl 2-(2-oxo-2-(pyrrolidin-1-yl)acetyl)phenylcarbamate (18):

Reaction was performed by following procedure B; N- Boc-isatin (0.2 g, 0.8097 mmol), proline (0.093 g, 0.8097 mmol) dry toluene (47ml), 4Å MS (200 mol%), time = 30 min, Yield = 65 %, white solid, **mp**. = 107 °C, **IR**: (neat) ν_{max}Broadband 3000 – 2887, 1732, 1635, 1514, 1446, 1249, 1145, 775 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.56 (brs, 1H), 8.5 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 3.64 (t, J = 6.9 Hz, 2H), 3.37 (t, J = 6.9 Hz, 2H), 1.94 (m, 4H), 1.52 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.2, 25.9, 28.4, 45.3, 46.7, 81.2, 117.1, 119.1, 121.5, 133.7, 136.7, 143.7, 152.9, 164.6, 195.4. TOF MS ES+ 341 (M+ Na). HRMS calcd. for $C_{17}H_{22}N_2O_4Na$ (M+Na) 341.1477 found 341.1516.

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Notes and references

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1. (a) L. M. Harwood, R. J. Vickers, in *Chemistry of Heterocyclic Compounds*, John Wiley & Sons, Inc., 2003, vol **59**, pp. 169-252; (b) L. M. Harwood, R. J. Vickers, In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, A. Padwa, H. W. Pearson, Eds.; John Wiley & Sons: New York, 2002; p 169. (c) A. Padwa, In *1,3-Dipolar Cycloaddition Chemistry*, John Wiley & Sons: New York, 1984; Vol. 2, p 277. (d) G. Pandey, P. Banerjee, and S. R. Gadre, *Chem. Rev.* 2006, **106**, 4484; (e) I. Coldham, and R. Hufton, *Chem. Rev.* 2005, **105**, 2765.
2. (a) K. V. Gothelf, and K. A. Jørgensen, *Chem. Rev.* 1998, **98**, 863; (b) K. V. Gothelf, in *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH, 2001, pp. 211.
3. S. Karlsson, H.-E. Högberg, *Org. Prep. Proced. Int.* 2001, **33**, 103.
4. C. Najera, and J. M. Sansano, *Curr. Org. Chem.* 2003, **7**, 1105.
5. J. P. A. Harrity, and O. Provoost, *Org. Bio. Chem.* 2005, **3**, 1349.
6. D. P. Curran, *Advances in cycloaddition.* **Vol 3**, JAI Press, Greenwich, Connecticut, 1993.
7. (a) C. Nájera, and J. M. Sansano, *Angew. Chem. Int. Ed. Engl* 2005, **44**, 6272. (b) H. W. Pearson, and P. Stoy, *Synlett.* 2003, 903.
8. A. Padwa, in *Comprehensive Organic Synthesis*, B. M. Trost, and I. Fleming, Eds,:Pergamon, Oxford, U.K., 1991, **4**, 1069.
9. R. Grigg, and V. Sridharan, in *Adnances in Cycloaddition* D. P. Curran, Ed.; JAI Press: Greenwich, CT, 1993, **3**, 161.
10. P. A. Wade, in *Comprehensive Organic Synthesis*, B. M. Trost, and I. Fleming,, Eds.; Pergamon: Oxford, U.K., 1991, **4**, 1111.
11. F. Shi, R.-Y. Zhu, X. Liang, and S.-J. Tu, *Adv. Synth. Catal* . 2013, **355**, 2447.
12. J. Danielsson, L. Toom, and P. Somfai, *Eur. J. Org. Chem.* 2011,**3**, 607.
13. A. M. D'Souza, N. Spiccia, J. Basutto, P. Jokisz, L. S. M. Wong, A. G. Meyer, A. B. Holmes, J. M. White, and J. H. Ryan, *Org. Lett.* 2010, **13**, 486.
14. (a) W.-J. Liu, X.-H. Chen, and L.-Z. Gong, *Org. Lett.* 2008, **10**, 5357; (b) A. Viso, R. Fernández de la Pradilla, A. García, C. Guerrero-Strachan, M. Alonso, M. Tortosa, A. Flores, M. Martínez-Ripoll, I. Fonseca, I. André, and A. Rodríguez, *Chem. -Eur. J.* 2003, **9**, 2867.
15. P. V. Guerra and V. A. Yaylayan, *J. Agric. Food Chem.* 2010, **58**, 12523.
16. (a) R. S. Kumar, S. M. Rajesh, S. Perumal, D. Banerjee, and P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem* 2010, **45**, 411. (b) WHO, Global Tuberculosis Report 2009, http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf.
17. D. Nozawa, T. Okubo, T. Ishii, H. Kakinuma, S. Chaki, S. Okuyama, and A. Nakazato, *Bioorg. Med. Chem.* 2007, **15**, 1989.
18. T. A. Martin, P. S. Prickett, A. G. Wheeler, and H. R. Williams, *J. Med. Chem.* 1963, **6**, 336.
19. W. T. Geiger, and H. F. Rase, *Ind. Eng. Chem. Res.* 1981, **20**, 688.
20. F. W. Short, and E. F. Elslager, *J. Med. Pharm. Chem.* 1962, **91**, 642.
21. R. Katritzky Alan, Z. Wang, and H. Lang, in *Heterocycl. Commun.* 1996, **2**, 109.
22. (a) M. J. Kornet, and A. P. Thio, *J. Med. Chem.* 1976, **19**, 892; (b) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y.

Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi, and R. Nagata, *J. Med. Chem.* 2001, **44**, 4641.
23. (a) K. Al Mamari, H. Ennajih, H. Zouihri, R. Bouhfid, S. W. Ng, and E. M. Essassi, *Tetrahedron Lett.* 2012, **53**, 2328. (b) K. Al Mamari, H. Ennajih, R. Bouhfid, E. M. Essassi, and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online* 2012, **68**, 1637. (c) K. Al Mamari, H. Ennajih, R. Bouhfid, E. M. Essassi, and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online* 2012, **68**, 1638. (d) K. Al Mamari, H. Ennajih, R. Bouhfid, E. M. Essassi, and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online* 2012, **68**, 1664.
24. (a) G. Pandey, P. Banerjee, R. Kumar, and V. G. Puranik, *Org.Lett.* 2005, **7**, 3713. (b) G. Pandey, R. Kumar, P. Banerjee, and V. G. Puranik, *Eur. J. Org. Chem.* 2011,**106**, 4571.
25. (a) S. U. Maheswari, K. Balamurugan, S. Perumal, P. Yogeeswari, and D. Sriram, *Bioorg. Med. Chem. Lett.* 2010, **20**, 7278; (b) A. Thangamani, *Eur. J. Med. Chem.* 2010, **45**, 6120.
26. http://preprint.chemweb.com/orgchem/0010004"..
27. A. Franke, *Liebigs Ann . Chem.* 1982, 794.
28. (a) A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648; (b) C. Lee, W. Yang, and R. G. Parr, *Phys. Rev. B: Condens.* 1988, **37**, 785.
29. Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. 31Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
30. (a) W. J. Hehre, L. Radom, P. V. R. Schleyer, and J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley: New York, 1986. (b) C. Gonzalez, and H. B. Schlegel, *J. Chem. Phys.* 1989, **90**, 2154.
31. (a) M. J. Aurell, L. R. Domingo, P. Pérez and R. Contreras, *Tetrahedron* 2004, **60**, 11503; (b) L. R. Domingo, *J. Org. Chem.* 1999, **64**, 3922; (c) A. Alvarez, E. Ochoa, Y. Verdecia, M. Suárez, M. Solá and N. Martín, *J. Org. Chem.* 2005, **70**, 3256; (d) K. Alimohammadi, Y. Sarrafi, M. Tajbakhsh, S. Yeganegi and M. Hamzehloueian, *Tetrahedron* 2011, **67**, 1589.
32. G. Chen, Y. Wang, X. Hao, S. Mu, and Q. Sun, *Chem Cent J* 2011, **5**, 37.
33. Y. M. Chung, J. H. Gong, and J. N. Kim, Bull. Korean Chem. Soc. 2002, **23**, 1363
34. K. Aikawa, S. Mimura, Y. Numata, and K. Mikami, Eur. J. Org. Chem. 2011, 62.

Graphical Abstract

Synthesis of Functionalized Dispiro-oxindoles through Azomethine Ylide Dimerization and Mechanistic Studies to Explain the Diastereoslectivity.

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Synthesis of functionalized dispirooxin-doles via [3 + 3]-cycloaddition of azo-methine ylide generated from condensat-ion of isatin and proline is reported. A transition state model for the origin of diastereoslectivity and mechanism of formation of these types of adducts is proposed.