NJC

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/njc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Facile construction of 3-indolochromenes and 3-indoloxanthenes via EDDF catalyzed one-pot three component reactions

Anuj Thakur, P. Linga Reddy, Mohit Tripathi and Diwan S. Rawat*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A novel and green strategy for the construction of biologically relevant 3-indolochromene and 3-indoloxanthene scaffolds is reported using EDDF as a catalyst and ethylene glycol as a promoter solvent. The catalytic system offers wider applicability, crossing over a variety of substrates, besides affording exclusively the desired product in shorter reaction times and high yields. Furthermore, the ease of work-up and purification combined with the recyclability of the EDDF-ethylene glycol system makes the present method environmentally sustainable and amenable to large-scale synthesis as well.

Introduction

Diversity oriented synthetic strategies are of vital importance for assembling medicinally important small chemical entities and multi-component reactions (MCRs) have emerged as a powerful tool for this purpose. MCRs are convergent cascade processes in which three or more starting materials react to form a product, where almost all of the atoms contribute to the newly formed product, essentially making the process green. MCRs with their inherent advantages *viz*. shorter reaction times, low manpower requirements, high atom-economies and simplified purification processes,[1] provide a unique way for optimizing the chemical space, contributing immensely towards the recently introduced concept of fragment based drug-design.[2,3] Indole is considered as a privileged scaffold for drug discovery,[4,5] as this electron-rich hetero-aromatic fragment is found to possess many important biological functions.[6] Likewise, chromenes and xanthenes are also medicinally significant heterocycles and recently, MCRs have been utilized for incorporating these fragments into diverse frameworks, with eventual identification of highly potent molecules, few of which are shown in figure 1.[7-10] Union of these biologically relevant scaffolds is likely to produce more active compounds and recently, the synthesis of 3-substituted indolo-pyrans *via* the one-pot MCR between salicylaldehyde, an active methylene compound (malonontrile/1,3-dicarbonyls) and indole utilizing a tandem Knoevenagel–Pinner-cyclization–Friedel-Crafts sequence, has gained much attention.[11,12]

However, the role of reaction-conditions for these one-pot processes is highly important and catalysts play a dynamic role in piloting the MCRs to their successful destination Accordingly, various catalysts have been used for the synthesis of 3-indolo-pyrans including metal salts ($FeCl_3$[13] and $InCl_3$[14]), metal-complexes (Cu(II)sulfonato-salen complex[15] and Zn(salphen) complex[16]), organo-catalysts (L-proline[17,18] and tetrabutylammonium-fluoride[19]) and ZnO nanoparticles.[20] However, most of these reported methods suffer from various drawbacks like use of toxic chemicals, additional step(s) for the preparation of catalyst which is cumbersome and expensive, undesirable side products, longer reaction times, tedious work-ups/purifications and non-recyclability of the catalyst.

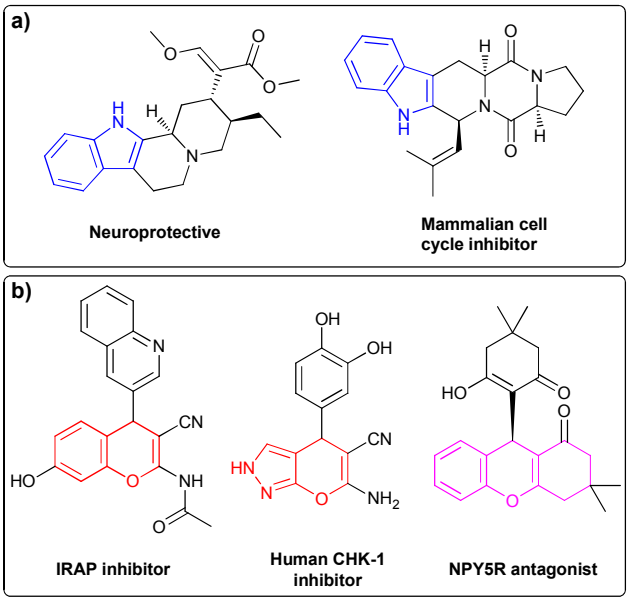
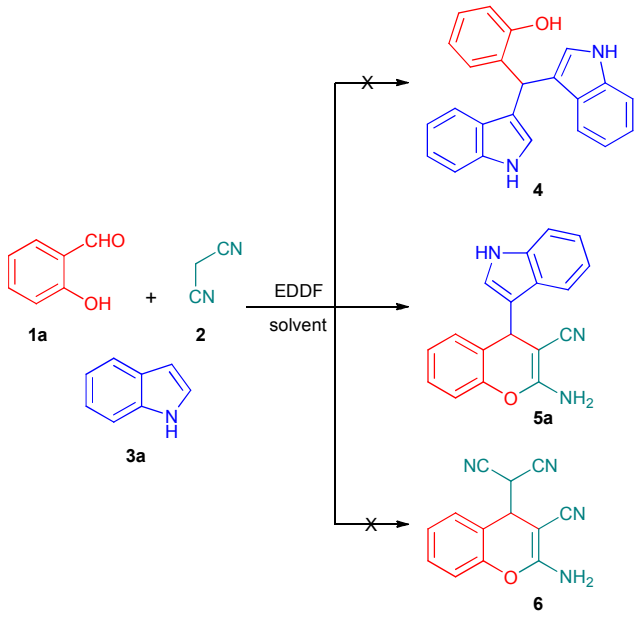


Fig. 1 Some medicinally important compounds containing a) indole and b) chromene/xanthene motifs.

As a part of our ongoing efforts towards the development of greener catalytic systems for important organic conversions,[21-28] we had recently explored the catalytic potential of EDDF (ethylenediammonium-diformate) for the synthesis of various 4*H*-pyrans.[29] In continuation of this work, and as a part of our broader objective of synthesizing biologically relevant molecules, we examined the effect of EDDF in the three-component, one-pot synthesis of various 3-substituted indolo-chromenes and indolo-xanthenes.

Results and discussion

For optimization of the reaction conditions for the synthesis of 3-indolochromenes, a model reaction with salicylaldehyde (**1a**), malononitrile (**2**), and indole (**3a**) was carried out (Scheme 1) initially with 20 mol% EDDF as a catalyst in the presence of different solvents at room temperature (Table 1). Solvents play a crucial role in making a process 'greener'[30] and hence, various environmentally-benign solvents (ethanol, ethylene glycol, PEG, glycerol and water) were screened and the reaction worked well with most of these solvents giving good yields of the desired indolochromene (**5a**). Ethylene glycol was recognized to be the best medium for this reaction (Table 1) and henceforth was used as a solvent of choice. Moreover, it was found that ethylene glycol alone can promote this reaction, though requiring a longer reaction time and offering a low yield (Table 1, entry 12). Hence, it was unambiguously used as a promoter medium for the subsequent reactions. The amount of EDDF was also reduced in a step-wise manner and it was observed that 5 mol% of the catalyst is sufficient for a satisfactory conversion.



Scheme 1 Synthesis of 3-indolochromene 5a via EDDF catalysed one-pot three component reaction.

Recently, Gu *et al.* have probed the conditions for selectivity of a similar type of MCR,[31] and on similar lines, roles of individual constituents of EDDF *viz.* ethylene-diamine and formic acid were experimentally investigated. Formic acid led to the appreciable formation of side-products **4** (29%) and **6** (20%), while the reaction took more time to complete in case of ethylene-diamine (entries 13-14, Table 1). On the other hand, EDDF yielded exclusively the desired product (**5a**) (see supplementary information), further demonstrating the efficacy of the EDDF-ethylene glycol system as a directing catalyst for this reaction. Hence, EDDF (150 mg) was mixed with ethylene glycol (10 ml) *via* ultra-sonication for 2h (Figure 2d), for its subsequent utilization as a catalytic system comprising of the catalyst (EDDF) and the promoter (ethylene glycol).

Table 1 Optimization of the reaction conditions for the synthesis of 3-indolochromene (**5a**)[a]

Entry	Catalyst (mol%)	Solvent	Time [min]	Yield [%][b]
1	EDDF (20)	EtOH	25	81
2	EDDF (20)	PEG_{600}	60	55
3	EDDF (20)	glycerol	15	86
4	EDDF (20)	DMSO	60	80
5	EDDF (20)	H_2O	30	79
6	EDDF (20)	Toluene	60	42
7	EDDF (20)	Neat	15	76
8	EDDF (20)	Ethylene glycol	15	87
9	EDDF (15)	Ethylene glycol	15	89
10	EDDF (10)	Ethylene glycol	15	91
11	EDDF (5)	Ethylene glycol	15	92
12	-	Ethylene glycol	180	43[c]
13	Formic acid (20)	Ethylene glycol	30	51[d]
14	Ethylene diamine (20)	Ethylene glycol	120	63

[a] Reaction conditions: salicylaldehyde **1a** (1 mmol), malononitrile **2** (1 mmol), indole **3a** (1 mmol), EDDF and solvent (0.5 mL) were stirred at rt for appropriate time. [b] Isolated yield. [c] Reaction was incomplete [d] Side-products **4** (29%) and **6** (20%) observed (calculated through ^{1}H NMR).

To study the expediency of the prepared EDDF-ethylene glycol system, the reaction was performed by employing different substituted salicylaldehydes (**1**), malononitrile (**2**) and various substituted indoles (**3**) for the synthesis of diverse indolochromenes (**5a-k,** Scheme 2). The results are summarized in Table 2. Almost all the substrates gave high yields (81-96%) of the desired indolochromenes and, in general, the reactions with *ortho*-vanillin (entries **5f-j**, Table-2) were faster compared to those with salicylaldehyde and a similar effect was observed with the use of 2-methylindole (entries **5b** and **5g**, Table-2). Furthermore, procedures for the work-up and purification were quite simple and in most of the cases a solid precipitate was obtained spontaneously. Otherwise, a small amount of water was added to the reaction-mixture to afford precipitation of the product (Figure 2) which was subsequently dried and purified *via* re-crystallization.

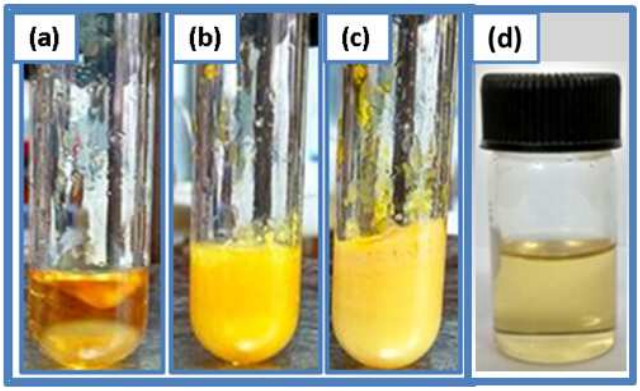
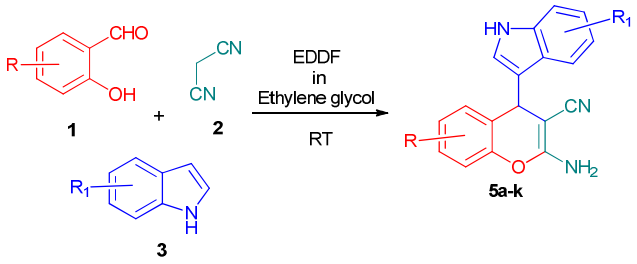


Fig. 2 Progress of the reaction for synthesis of **5a**: (a) reaction-mixture at the onset of reaction, (b) during the reaction, (c) after completion of the reaction (solid precipitate was obtained); (d) EDDF-ethylene glycol system



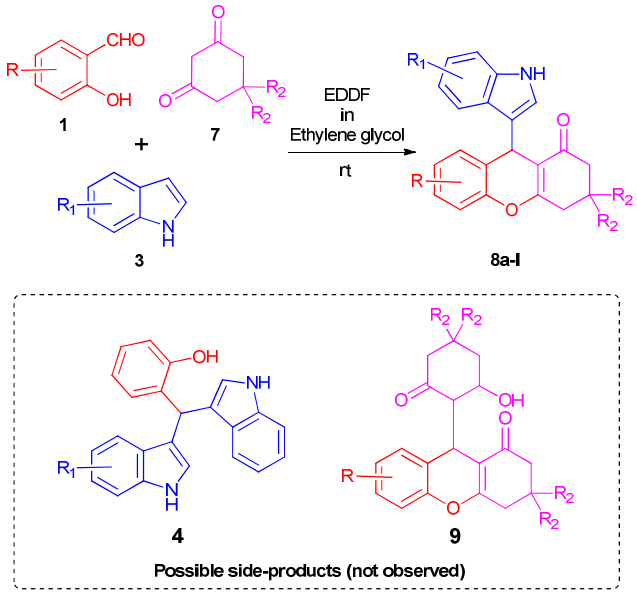
Scheme 2 Synthesis of 3-indolochromenes (**5a-k**)

Table 2 EDDF-ethylene glycol catalysed one-pot three-component synthesis of various 3-indolochromenes (**5a-k**) at room temperature.[a]

Entry	R	R_1	Time (min)	Yield (%)[b]	Observed mp (°C)	Literature mp (°C)
5a	H	H	15	92	187-189	195-196[32]
5b	H	2-Me	15	91	200-202	186-189[33]
5c	H	5-OMe	25	87	182-184	199-201[15]
5d	H	5-Br	35	90	166-168	160-162[15]
5e	H	1-Me	30	81	202-204	202[14]
5f	3-OMe	H	14	93	222-224	215-216[17]
5g	3-OMe	2-Me	12	96	239-241	-
5h	3-OMe	5-OMe	16	93	201-203	-
5i	3-OMe	5-Br	23	89	218-220	-
5j	3-OMe	1-Me	18	88	223-225	-
5k	4-OH	H	27	87	208-210	-

[a] Substituted salicylaldehyde **1** (1 mmol), malononitrile **2** (1 mmol), indole(s) **3** (1 mmol) and EDDF-ethylene glycol (0.5 mL) stirred at rt. [b] Isolated yield.

Next, in order to inspect the versatility of EDDF-ethylene glycol system, we replaced malononitrile (**2**) with 1,3-dicarbonyls such as dimedone (**7**, R_2 = Me) or 1,3-cyclohexadione (**7**, R_2 = H), which resulted in the formation of desired substituted 3-indoloxanthenes **8a-l** (Scheme 3). The reactions proceeded smoothly and gave high yields in short reaction times (15-35 min) at ambient temperature (Table 3).



Scheme 3 Synthesis of 3-indoloxanthenes (**8a-l**)

In the case of this MCR also, possibility of formation of side-products *viz.* bisindole **4** and **9** persists (Scheme 3) as previously reported.[18] However, the present protocol lead to exclusive formation of the desired 3-indoloxanthene product which was confirmed by the spectroscopic analyses of the reaction crude (**8a**) which ruled out any by-products and the data conformed well to that reported in literature (see supplementary information). As before, the work-up/purification was convenient, and in most of the cases, a solid precipitate of the desired product was obtained.

Table 3 Synthesis of various 3-indoloxanthenes (**8a-l**) catalysed by EDDF in ethylene glycol at room temperature[a]

Entry	R	R_1	R_2	Time (min)	Yield (%)[b]	Observed mp (°C)	Literature mp (°C)
8a	H	H	H	15	87	233-235	-
8b	H	2-Me	H	21	89	210-212	-
8c	H	5-OMe	H	40	85	182-184	-
8d	H	1-Me	H	35	81	213-215	-
8e	H	5-Br	H	25	83	205-207	-
8f	3-OMe	H	H	25	96	247-249	-
8g	3-OMe	2-Me	H	20	97	255-257	-
8h	3-OMe	1-Me	H	30	95	244-246	-
8i	3-OMe	5-OMe	H	20	91	252-254	-
8j	3-OMe	5-Br	H	25	85	263-265	-
8k	H	H	Me	17	94	197-199	189-191[21]
8l	3-OMe	H	Me	12	90	110-112	106-108[13]

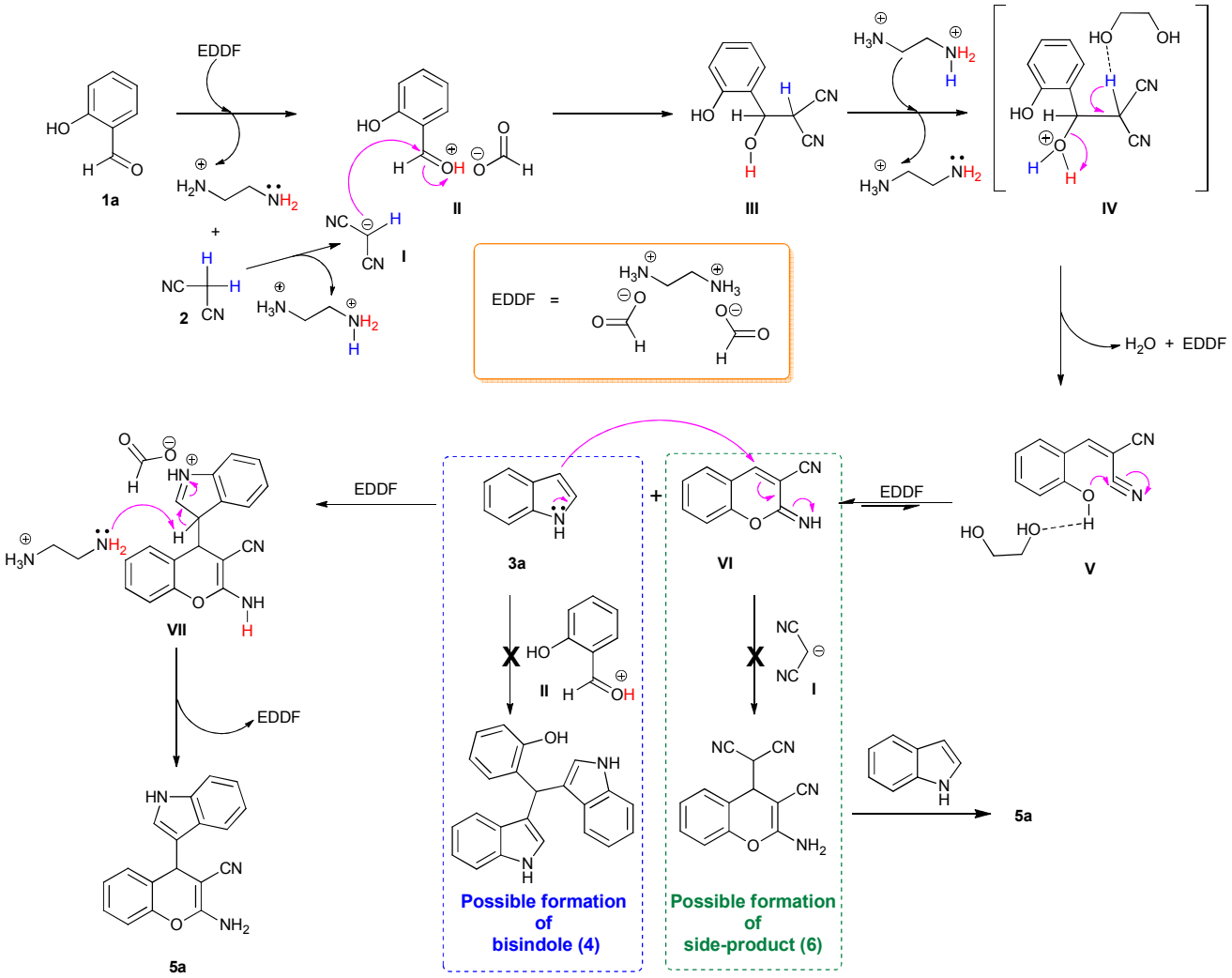
[a] Substituted salicylaldehyde **1** (1 mmol), dimedone or 1,3-cyclohexadione **7** (1 mmol), indole(s) **3** (1 mmol) and EDDF-ethylene glycol (0.5 mL) stirred at rt. [b] Isolated yield.

The superiority of EDDF-ethylene glycol over other catalysts reported for the synthesis of 3-indolochromene (**5a**) or 3-indoloxanthene (**8k**) is further established by a comparative study presented in Table 4. It clearly shows that the present method works in ambient temperature and in the shortest reaction time, while at the same time offering the best TON (turnover number) and TOF (turnover frequency) values than all the other reported catalytic systems for the synthesis of 3-indolopyrans **5a** or **8k**.

Table 4 Comparative study of methods for the synthesis of 3-indolo-chromene (**5a**) or 3-indoloxanthene (**8k**)

Catalyst/ additive/ solvent	T	Time (min)	Yield (%)	Mol%	TON	TOF (min^{-1})	Ref
TBAF	60 °C	40	88	10	8.80	0.22	19
ZnO nanoparticles	55 °C	40, 50*	90, 91*	10	9.00, 9.10*	0.225, 0.18*	21
KH_2PO_4, ethylene glycol	rt	1680	90	100	0.90	0.00053	34
(S)-Proline, EtOH	80 °C	480	80	10	8.00	0.016	17
$InCl_3$, H_2O	rt	72	84	20	4.20	0.058	14
(S)-Proline, SDS, H_2O	rt*	120*	95*	10	9.50*	0.079*	18
$FeCl_3$, PPh_3 , DCE	80*	660*	81*	10	8.10*	0.012*	13
EDDF-ethylene glycol	rt	15, 17*	92, 94*	5	18.40, 18.80*	1.22, 1.10*	Present

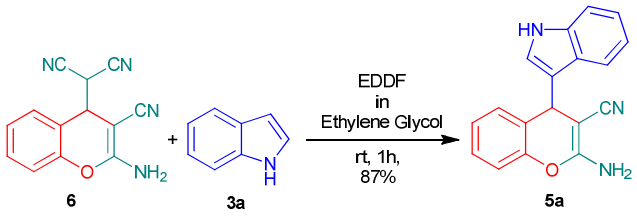
* For 3-indoloxanthene **8k**.



Scheme 4 Plausible mechanism for the synthesis of 3-indolochromenes *via* EDDF-ethylene glycol catalysed one-pot three component reaction.

A plausible mechanism, illustrating the role of EDDF and ethylene glycol in the synthesis of indolochromenes is proposed in scheme 4. Recently, an ambiphilic dual activation role has been suggested for various catalysts including ionic liquids.[35-38] EDDF is a salt and hence, on similar lines, it can act as an ambiphilic catalyst[29] wherein both the cation and anion act cooperatively as an electrophile and nucleophile. The acidic part increases the electrophilicity of the carbonyl group of **1a** at one side while the transiently generated amine aids in the formation and subsequent attack of the malonate ion (**I**) from the other end. Subsequent protonation and removal of water molecule results in the formation of the initial knoevenagel adduct (**V**) which gets cyclized to the 2-iminochromene intermediate (**VI**) *via* a Pinner reaction. The formation of intermediate **VI** was further confirmed by the peak at 171.0551 in the mass spectrum (refer supplementary information) of the crude product (**5a**). Another possibility was that two molecules of indole (**3a**) could have directly reacted with the protonated aldehyde (**II**) to yield the bisindole by-product (**4**) as illustrated within the dashed blue-rectangle in scheme 4. However, the formation of bis(indolyl)methane is known to be acid-catalysed and in case of EDDF, the conjugate acid (ethylenediammonium ion) is a weak acid, so the formation of **4** is not favoured. Conversely, when formic acid (relatively stronger acid) was used as a catalyst (Table 1), appreciable formation of bisindole **4** was also observed. Ethylene glycol is also known to promote various important reactions *via* H-bonding,[24,39] which in turn, may aid in the polarization and stabilization of various reaction intermediates (**IV** and **V**) in the overall sequence of the mechanism. Furthermore, EDDF catalyzes the ensuing Friedel-Crafts alkylation of indole (**3a**) with the 2-iminochromene intermediate (**VI**) resulting in the formation of the desired 3-indolochromene (**5a**), as shown in the mechanism (Scheme 4). Another possibility was of a nucleophilic attack of malonate (**I**) to **VI** leading to the formation of by-product **6** (as shown in green dashed rectangle, scheme 4). However, it was envisaged that indole **3a** may react with by-product **6** to yield the desired 3-indolochromene **5a** by replacing the malonate. A similar reaction between indole and dimedone-xanthene by-product has been studied by Gu *et al.*[13] To experimentally verify this notion, we investigated the reaction between pre-formed **6** (1 mmol) and indole **3a** (1 mmol) using EDDF-ethylene glycol as a catalyst

(Scheme 5). It was found that **6** was completely consumed in the reaction and the desired 3-indolocromene **5a** was formed as a sole product, thereby verifying our perceived thought. Hence, on the basis of these observations, we can assume that any transiently generated by-product **6** was apparently replaced by the indole **3a** to yield the desired product **5a** leading to the exclusive formation of desired 3-indolochromenes by EDDF-ethylene glycol catalytic system in the concerned MCR .



Scheme 5 Reaction of **6** with indole **3a**.

Recyclability of the EDDF-ethylene glycol system was also studied using the model one pot reaction of salicylaldehyde, malononitrile and indole (entry 5a, Table 2). After completion of the reaction, water was added to the reaction mixture. The precipitated product was filtered and the filtrate containing water and the catalytic system was concentrated under reduced pressure. The residue was washed with diethylether and after drying it was ready to be used for the subsequent run. The recycled EDDF-ethylene glycol system was re-used at least six times without showing any considerable loss in yield (Figure 3).

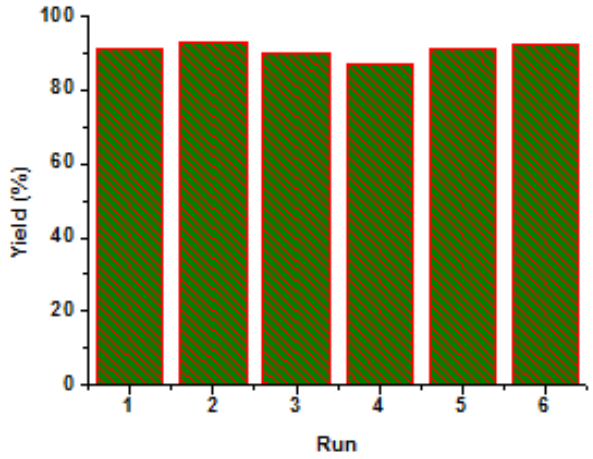


Fig. 3 Reusability study of EDDF-ethylene glycol catalytic system for the synthesis of **5a**.

Conclusions

In summary, EDDF in ethylene glycol was developed as an efficacious catalytic system for the greener synthesis of different 3-indolochromenes and 3-indoloxanthenes at lower reaction times and ambient temperatures. The most remarkable point for the EDDF-ethylene glycol catalyst system was generation of the desired product in high yields without any unwarranted side-products, besides the ease of work-up and purification. Further, the catalyst was recycled and showed no appreciable loss in reaction yields for the subsequent runs. Also, EDDF showed much better TON and TOF parameters for the synthesis of 3-indolochromene/3-indoloxanthene than the previously reported catalysts. Moreover, being inexpensive to produce, non-hazardous and owing to its simplicity and amenability to large scale operation, it provides an effective way to assemble two medicinally significant fragments *viz.* indoles and chromenes/xanthenes. Further applicability of EDDF in catalyzing important organic reactions is under investigation by our lab.

Experimental

All reagents were purchased from Merck and Aldrich and were used as such. Reaction progress was monitored using pre-coated TLC plates (E. Merck Kieselgel 60 F254) and spots were visualised under UV light and also by exposing TLC plates to iodine vapour. ^{1}H NMR and ^{13}C NMR spectra were taken on a Jeol Spectrospin spectrometer at 400 MHz and 100 MHz respectively using TMS as an internal standard. Melting points were recorded in open capillary tubes on an ERS automated melting point apparatus and are uncorrected. Mass spectra were recorded on Agilent Accurate Mass Q-TOF MS system or micromass LCT Mass Spectrometer/Data system. IR spectra were recorded using Perkin-Elmer and Bruker FT-IR in the range of 4000–400 cm^{-1} and only characteristic frequencies are expressed. EDDF was prepared according to the procedure reported previously.[21]

General procedure for the synthesis of 3-indolochromenes (5a-k) and 3-indoloxanthenes (8a-l):

To a mixture of substituted salicylaldehyde (1 mmol), malononitrile (1 mmol) and various indoles (1 mmol) in a 10 mL round bottom flask, was added 0.5 mL of EDDF-ethylene glycol and the mixture was stirred at room temperature for the stipulated period of time. After completion of the reaction (TLC), 5 mL water was added to afford precipitation of the product which was subsequently filtered-off, washed with water (20 mL) and dried in vacuo at 50 ^{o}C. The crude product was recrystallized from ethanol to yield the respective 3-indolochromene. 3-Indoloxanthenes (**8a-l**) were prepared in a similar manner but by replacing malononitrile (2) with cyclohexadienone or dimedone (7).

Spectral data for selected indolo-chromenes:

2-Amino-4-(5-methoxy-*1H*-indol-3-yl)-*4H*-chromene-3-carbonitrile (5c): IR (cm^{-1}, Film): 3442, 3314, 2937, 2191, 1654, 1581, 1485, 1395, 1348, 1262, 1220, 1171, 1106, 1025, 839, 755, 606; ^{1}H NMR (400 MHz, $CDCl_3$): 3.73 (s, 3H), 4.56 (br s, 2H), 5.02 (s, 1H), 6.77-6.82 (m, 2H), 6.97-7.03 (m, 2H), 7.08-7.11 (m, 2H), 7.16-7.18 (m, 1H), 7.20-7.22 (m, 1H), 7.95 (br s, 1H); ESI-MS (m/z): 318.13 $(MH)^+$; Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24; Found: C, 71.99; H, 4.87; N, 13.19.

2-Amino-4-(*1H*-indol-3-yl)-8-methoxy-*4H*-chromene-3-carbonitrile (5f): IR (cm^{-1}, Film): 3408, 3344, 2940, 2840, 2190, 1637, 1579, 1480, 1414, 1326, 1268, 1217, 1125, 1076, 950, 745; ^{1}H NMR (400 MHz, DMSO-d_6): 3.81 (s, 3H), 4.94 (s, 1H), 6.61 (dd, 1H, J = 7.32 Hz, J = 1.22 Hz), 6.78 (br s, 2H), 6.83-6.92 (m, 3H), 6.98-7.02 (m, 1 H), 7.22-7.25 (m, 2H), 7.31 (d, 1H, J = 7.93 Hz), 10.88 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 32.54,

55.65, 56.23, 110.28, 111.64, 118.39, 118.69, 120.32, 120.75, 120.94, 122.92, 123.90, 124.49, 125.19, 136.83, 137.84, 146.86, 159.96; ESI-MS (m/z): 318.12 $(MH)^+$.

2-Amino-8-methoxy-4-(2-methyl-*1H*-indol-3-yl)-*4H*-chromene-3-carbonitrile (5g): IR (cm^{-1}, Film): 3468, 3390, 3325, 2935, 2835, 2195, 1655, 1583, 1459, 1399, 1278, 1213, 1187, 1078, 954, 748, 627; ^1H NMR (400 MHz, DMSO-d_6): 2.40 (s, 3H), 3.80 (s, 3H), 5.00 (s, 1H), 6.44-6.46 (m, 1H), 6.70 (br s, 2H), 6.74-6.78 (m, 1H), 6.85-6.92 (m, 3H), 6.99 (d, 1H, J = 7.93 Hz), 7.19 (d, 1H, J = 7.93 Hz), 10.79 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 11.19, 30.99, 55.58, 56.05, 110.17, 110.54, 113.86, 117.35, 118.20, 119.93, 120.35, 120.68, 123.88, 124.18, 126.49, 131.96, 135.29, 137.94, 146.73, 159.52; ESI-MS (m/z): 332.15 $(MH)^+$; Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68; Found: C, 72.51; H, 5.19; N, 12.75.

2-Amino-8-methoxy-4-(5-methoxy-*1H*-indol-3-yl)-*4H*-chromene-3-carbonitrile (5h): IR (cm^{-1}, Film): 3463, 3318, 3184, 2937, 2837, 2206, 1660, 1584, 1482, 1435, 1402, 1327, 1268, 1210, 1169, 1080, 955, 843, 768, 636; ^1H NMR (400 MHz, DMSO-d_6): 3.63 (s, 3H), 3.80 (s, 3H), 4.90 (s, 1H), 6.63-6.69 (m, 2H), 6.75-6.76 (m, 1H), 6.79 (br s, 2 H), 6.85-6.93 (m, 2H), 7.15-7.17 (m, 1H), 7.20 (d, 1H, J = 9.16 Hz), 10.70 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 32.42, 55.09, 55.68, 56.09, 100.90, 110.31, 110.39, 112.13, 118.59, 120.33, 120.81, 123.43, 123.91, 124.61, 125.56, 131.96, 137.92, 146.88, 152.70, 160.13; HRMS (ESI, M/Z) calcd for $C_{20}H_{18}N_3O_3$: 348.1343 $(MH)^+$; Found: 348.1338.

2-Amino-4-(5-bromo-*1H*-indol-3-yl)-8-methoxy-*4H*-chromene-3-carbonitrile (5i): IR (cm^{-1}, Film): 3386, 3327, 2935, 2837, 2188, 1720, 1654, 1586, 1406, 1332, 1214, 1187, 1090, 1041, 958, 885, 791; ^1H NMR (400 MHz, DMSO-d_6): 3.79 (s, 3H), 4.93 (s, 1H), 6.57 (d, 1H, J = 7.33 Hz), 6.86-6.92 (m, 4H), 7.11 (dd, 1H, J = 8.70 Hz, J = 1.83 Hz), 7.28 (d, 1H, J = 8.70 Hz), 7.31 (d, 1H, J = 2.29 Hz), 7.34 (d, 1H, J = 1.83 Hz), 11.12 (br s, 1H); ESI-MS (m/z): 396.04 $(MH)^+$, 398.03 $(MH+2)^+$; Anal. Calcd for $C_{19}H_{14}BrN_3O_2$: C, 57.59; H, 3.56; N, 10.60; Found: C, 57.63; H, 3.59; N, 10.66.

2-Amino-8-methoxy-4-(1-methyl-*1H*-indol-3-yl)-*4H*-chromene-3-carbonitrile (5j): IR (cm^{-1}, Film): 3439, 3321, 2937, 2840, 2189, 1647, 1581, 1479, 1399, 1328, 1279, 1203, 1184, 1082, 947, 764, 740; ^1H NMR (400 MHz, DMSO-d_6): 3.72 (s, 3H), 3.80 (s, 3H), 4.94 (s, 1H), 6.62 (dd, 1H, J = 7.32 Hz, J = 1.83 Hz), 6.79 (br s, 2H), 6.85-6.93 (m, 3H), 7.06-7.10 (m, 1H), 7.20-7.22 (m, 1H), 7.29 (d, 1H, J = 7.93 Hz), 7.35 (d, 1H, J = 7.93 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 32.23, 32.31, 55.64, 56.10, 109.83, 110.30, 118.12, 118.58, 120.27, 120.74, 121.08, 123.92, 124.47, 125.55, 127.18, 137.12, 137.79, 146.87, 159.98; HRMS (ESI, M/Z) calcd for $C_{20}H_{18}N_3O_2$: 332.1394 $(MH)^+$; Found: 332.1391.

2-Amino-7-hydroxy-4-(2-methyl-*1H*-indol-3-yl)-*4H*-chromene-3-carbonitrile (5k): IR (cm^{-1}, Film): 3482, 3427, 3345, 2185, 1653, 1507, 1459, 1400, 1324, 1295, 1146, 1108, 1044, 851, 752; ^1H NMR (400 MHz, DMSO-d_6): 2.40 (s, 3H), 4.90 (s, 1H), 6.37-6.39 (m, 2H), 6.62 (br s, 2H), 6.67-6.69 (m, 1H), 6.74-6.77 (m, 1H), 6.89-6.92 (m, 1H), 6.97 (d, 1H, J = 7.93 Hz), 7.20 (d, 1H, J = 7.93 Hz), 9.55 (br s, 1H), 10.75 (br s, 1H); HRMS (ESI, M/Z) calcd for $C_{19}H_{16}N_3O_2$: 318.1237 $(MH)^+$; Found: 318.1232.

Spectral data for indolo-xanthenes:

9-(*1H*-indol-3-yl)-2,3,4,9-tetrahydro-*1H*-xanthen-1-one (8a): IR (cm^{-1}, Film): 2922, 2877, 1641, 1484, 1455, 1374, 1330, 1238, 1131, 1061, 993, 858, 762, 630; ^1H NMR (400 MHz, $CDCl_3$): 1.88-2.08 (m, 2H), 2.30-2.41 (m, 2H), 2.59-2.78 (m, 2H), 5.34 (s, 1H), 6.95-7.00 (m, 2H), 7.06-7.18 (m, 5H), 7.24-7.27 (m, 1H), 7.39 (d, 1H, J = 7.79 Hz), 8.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.49, 27.93, 29.52, 37.15, 111.28, 114.14, 116.26, 119.18, 119.47, 120.65, 121.69, 122.60, 125.00, 125.41, 125.83, 127.50, 130.20, 136.58, 149.72, 166.13, 197.45; HRMS (ESI, M/Z) calcd for $C_{21}H_{18}NO_2$: 316.1332 $(MH)^+$; Found: 316.1332.

9-(2-Methyl-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8b): IR (cm^{-1}, Film): 3396, 2951, 2872, 1633, 1580, 1485, 1373, 1227, 1180, 995, 863, 740, 665; ^1H NMR (400 MHz, $CDCl_3$): 1.90-2.02 (m, 2H), 2.28-2.31 (m, 2H), 2.60 (s, 3H), 2.71-2.78 (m, 2H), 5.24 (s, 1H), 6.86-6.90 (m, 1H), 6.92-6.98 (m, 2H), 7.01-7.11 (m, 3H), 7.13-7.15 (m, 1H), 7.19-7.21 (m, 1H), 7.78 (br s, 1H); ESI-MS (m/z): 330.16 $(MH)^+$; Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25; Found: C, 80.31; H, 5.89; N, 4.33.

9-(5-Methoxy-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8c): IR (cm^{-1}, Film): 3432, 2931, 2826, 1647, 1487, 1457, 1373, 1224, 1171, 1057, 993, 797, 759, 622; ^1H NMR (400 MHz, $CDCl_3$): 1.90-2.02 (m, 2H), 2.29-2.38 (m, 2H), 2.58-2.71 (m, 2H), 3.74 (s, 3H), 5.32 (s, 1H), 6.73 (dd, 1H, J = 8.54 Hz, J = 2.44 Hz), 6.87 (d, 1H, J = 1.83 Hz), 6.99-7.02 (m, 1H), 7.09-7.20 (m, 5H), 7.89 (br s, 1H); HRMS (ESI, M/Z) calcd for $C_{22}H_{20}NO_3$: 346.1438 $(MH)^+$; Found: 346.1425.

9-(1-Methyl-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8d): IR (cm^{-1}, Film): 3414, 2922, 2825, 1638, 1466, 1375, 1229, 1174, 1131, 992, 857, 747, 618; ^1H NMR (400 MHz, $CDCl_3$): 1.89-2.07 (m, 2H), 2.32-2.37 (m, 2H), 2.62-2.78 (m, 2H), 3.68 (s, 3H), 5.32 (s, 1H), 6.94-6.99 (m, 3H), 7.07-7.14 (m, 3H), 7.17-7.20 (m, 2H), 7.39 (d, 1H, J = 7.93 Hz); ESI-MS (m/z): 330.15 $(MH)^+$; Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25; Found: C, 80.29; H, 5.93; N, 4.31.

9-(5-Bromo-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8e): IR (cm^{-1}, Film): 3299, 2925, 2861, 1630, 1457, 1376, 1225, 1180, 1135, 1101, 996, 882, 754, 620; ^1H NMR (400 MHz, $CDCl_3$): 1.95-2.05 (m, 2H), 2.35-2.47 (m, 2H), 2.61-2.79 (m, 2H), 5.29 (s, 1H), 6.98-7.02 (m, 1H), 7.09-7.20 (m, 6H), 7.51-7.53 (m, 1H), 8.15 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.40, 27.81, 29.22, 37.04, 112.64, 112.72, 113.74, 116.34, 120.35, 121.65, 123.75, 124.48, 124.87, 125.01, 127.42, 127.64, 129.94, 135.03, 149.43, 166.33, 197.50; ESI-MS (m/z): 394.04 $(MH)^+$, 396.04 $(MH+2)^+$.

9-(*1H*-Indol-3-yl)-5-methoxy-2,3,4,9-tetrahydro-xanthen-1-one (8f): IR (cm^{-1}, Film): 3369, 2922, 2851, 1610, 1376, 1272, 1223, 1184, 1133, 1090, 743; ^1H NMR (400 MHz, $CDCl_3$): 1.91-2.04 (m, 2H), 2.32-2.37 (m, 2H), 2.66-2.86 (m, 2H), 3.93 (s, 3H), 5.33 (s, 1H), 6.72-6.78 (m, 2H), 6.90-6.94 (m, 1H), 6.96-7.00 (m, 1H), 7.06-7.10 (m, 1H), 7.12 (d, 1H, J = 2.44 Hz), 7.25-7.27 (m, 1H), 7.45 (d, 1H, J = 7.93 Hz), 8.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.45, 27.84, 29.41, 37.05, 56.06, 109.63, 111.18, 114.01, 119.12, 119.40, 120.40, 121.60, 122.50, 124.54, 125.74,

126.42, 136.49, 139.23, 147.48, 165.84, 197.38; ESI-MS (m/z): 346.14 $(MH)^+$.

5-Methoxy-9-(2-methyl-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8g): IR (cm^{-1}, Film): 3396, 2924, 2852, 1637, 1611, 1584, 1460, 1376, 1272, 1222, 1184, 1089, 933, 755; ^1H NMR (400 MHz, $CDCl_3$): 1.90-2.06 (m, 2H), 2.29-2.33 (m, 2H), 2.63 (s, 3H), 2.65-2.75 (m, 1H), 2.81-2.89 (m, 1H), 3.92 (s, 3H), 5.24 (s, 1H), 6.63 (d, 1H, J = 7.93 Hz), 6.70 (dd, 1H, J = 7.93 Hz, J = 1.22 Hz), 6.85-6.92 (m, 2H), 6.96-7.00 (m, 1H), 7.16 (d, 1H, J = 7.93 Hz), 7.23-7.25 (m, 1H), 7.75 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.99, 20.51, 27.77, 28.50, 37.03, 56.07, 109.46, 110.22, 113.39, 115.62, 117.91, 119.17, 120.43, 121.58, 124.46, 126.25, 127.04, 131.37, 135.18, 139.10, 147.31, 165.55, 197.49; ESI-MS (m/z): 360.17 $(MH)^+$; Anal. Calcd for $C_{23}H_{21}NO_3$: C, 76.86, H, 5.89; N, 3.90; Found: C, 76.91; H, 5.95; N, 3.88.

5-Methoxy-9-(1-methyl-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8h): IR (cm^{-1}, Film): 3440, 2932, 2839, 1645, 1583, 1483, 1373, 1220, 1183, 1092, 935, 741, 647; ^1H NMR (400 MHz, DMSO-d_6): 1.90-2.07 (m, 2H), 2.32-2.36 (m, 2H), 2.65-2.73 (m, 1H), 2.80-2.87 (m, 1H), 3.67 (s, 3H), 3.92 (s, 3H), 5.30 (s, 1H), 6.73 (d, 1H, J = 7.93 Hz), 6.77 (d, 1H, J = 7.93 Hz), 6.94-7.00 (m, 2H), 7.09-7.13 (m, 1H), 7.18 (d, 1H, J = 7.93 Hz), 7.45 (d, 1H, J = 7.93 Hz), 10.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.42, 27.80, 29.17, 32.56, 37.03, 56.05, 109.15, 109.49, 114.20, 118.85, 118.95, 119.21, 121.11, 121.53, 124.51, 126.12, 126.60, 127.12, 137.09, 139.19, 147.45, 165.66, 197.28; ESI-MS (m/z): 360.16 $(MH)^+$.

5-Methoxy-9-(5-methoxy-*1H*-indol-3-yl)-2,3,4,9-tetrahydro-xanthen-1-one (8i): IR (cm^{-1}, Film): 3317, 2952, 2824, 1639, 1581, 1485, 1375, 1221, 1182, 1093, 924, 826, 735, 631; ^1H NMR (400 MHz, $CDCl_3$): 1.91-2.08 (m, 2H), 2.29-2.24 (m, 2H), 2.65-2.75 (m, 1H), 2.77-2.85 (m, 1H), 3.78 (s, 3H), 3.92 (s, 3H), 5.30 (s, 1H), 6.73-6.79 (m, 3H), 6.93 (d, 1H, J = 7.93 Hz), 6.96-6.97 (m, 1H), 7.04 (d, 1H, J = 2.44 Hz), 7.14 (d, 1H, J = 8.54 Hz), 7.89 (br s, 1H); ESI-MS (m/z): 376.16 $(MH)^+$; Anal. Calcd for $C_{23}H_{21}NO_4$: C, 73.58; H, 5.64; N, 3.73; Found: C, 73.63; H, 5.72; N, 3.81.

9-(5-Bromo-*1H*-indol-3-yl)-5-methoxy-2,3,4,9-tetrahydro-xanthen-1-one (8j): IR (cm^{-1}, Film): 3321, 2932, 2837, 1642, 1583, 1483, 1380, 1217, 1185, 1092, 937, 882, 759, 645; ^1H NMR (400 MHz, DMSO-d_6): 1.83-2.03 (m, 2H), 2.20-2.36 (m, 2H), 2.65-2.78 (m, 2H), 3.82 (s, 3H), 5.16 (s, 1H), 6.82 (d, 1H, J = 7.93 Hz), 6.87 (d, 1H, J = 7.93 Hz), 6.94-6.98 (m, 1H), 7.09-7012 (m, 2H), 7.24 (d, 1H, J = 8.54), 7.67 (d, 1H, J = 1.22 Hz), 11.03 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 20.14, 27.17, 28.02, 28.09, 36.53, 55.68, 55.75, 110.13, 111.20, 113.11, 113.51, 119.74, 120.72, 123.25, 124.51, 126.48, 127.17, 134.92, 138.37, 147.33, 166.08, 196.21; ESI-MS (m/z): 424.05 $(MH)^+$, 426.06 $(MH+2)^+$; Anal. Calcd for $C_{22}H_{18}BrNO_3$: C, 62.28; H, 4.28; N, 3.30; Found: C, 62.34; H, 4.31; N, 3.38.

Acknowledgements

DSR thanks DST (Department of Science & Technology, Govt. of India) and the University of Delhi, Delhi, India for financial assistance in the form of DU-DST-PURSE grant and DU R&D grant. AT, PLR and MT are thankful to CSIR, UGC and DST for the award of senior research fellowship, senior research fellowship and INSPIRE-senior research fellowship, respectively. We are thankful to USIC-CIF, University of Delhi, for analytical data.

Notes and references

[a] *Department of Chemistry, University of Delhi, Delhi-110007, India. Fax: +91-11-27667501; Tel: 91-11-27662683; E-mail: dsrawat@chemistry.du.ac.in;*

† Electronic Supplementary Information (ESI) available: [Discussion and ^1H NMR, HRMS spectra of reaction-crude (**5a** and **8a**) for exclusive formation of desired product] See DOI: 10.1039/b000000x/

1 B. B. Shingate, *Organic Chem. Curr. Res*., 2012, **1**, 3.
2 D. A. Erlanson, R. S. McDowell and T. O'Brien, *J. Med. Chem*., 2004, **47**, 3463.
3 P. J. Hajduk and J. Greer, *Nat. Rev. Drug Discov*., 2007, **6**, 211.
4 M. E Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol*., 2010, **14**, 347.
5 R.W. DeSimone, K.S. Currie, S.A. Mitchell, J.W. Darrow and D.A. Pippin, *Comb. Chem. High T. Scr*., 2004, **7**, 473.
6 D. S. Bhakuni and D. S. Rawat, Bioactive marine natural product, springer, New York, USA and Anamaya Publisher, New Delhi, India, ISBN: 1-4020-3472-5 (2005).
7 L. Weber, *Curr. Med. Chem*., 2002, **9**, 124.
8 S. J. Mountford, A. L. Albiston, W. N. Charman, L. Ng, J. K. Holien, M. W. Parker, J. A. Nicolazzo, P. E. Thompson and S. Y. Chai, *J. Med. Chem*., 2014, **57**, 1368.
9 N. Foloppe, L. M. Fisher, R. Howes, A. Potter, A. G. S. Robertson and A. E. Surgenor, *Bioorg. Med. Chem*., 2006, **14**, 4792.
10 N. Sato, M. Jitsuoka, T. Shibata, T. Hirohashi, K. Nonoshita, M. Moriya, Y. Haga, A. Sakuraba, M. Ando, T. Ohe, H. Iwaasa, A. Gomori, A. Ishihara, A. Kanatani, and T. Fukami, *J. Med. Chem*., 2008, **51**, 4765.
11 I. B. Masesane and Z. Y. Desta, *Beilstein J. Org. Chem*., 2012, **8**, 2166.
12 Y. F. Han and M. Xia, *Curr. Org. Chem*., 2010, **14**, 379.
13 M. Li and Y. Gu, *Adv. Synth. Catal*., 2012, **354**, 2484.
14 G. Shanthi and P. T. Perumal, *Tetrahedron Lett*., 2007, **48**, 6785.
15 Y. Qu, F. Ke, L. Zhou, Z. Li, H. Xiang, D. Wu and X. Zhou, *Chem. Commun*., 2011, **47**, 3912.
16 D. Anselmo, E. C. Escudero-Adán, M. M. Belmonte and A. W. Kleij, *Eur. J. Inorg. Chem*., 2012, **29**, 4694.
17 M. Li, B. Zhang and Y. Gu, *Green Chem*., 2012, **14**, 2421.
18 N. C. Ganguly, S. Roy, P. Mondal and R. Saha, *Tetrahedron Lett*., 2012, **53**, 7067.
19 N. Singh, B. K. Allam, D. S. Raghuvanshi and K. N. Singh, *Adv. Synth. Catal*., 2013, **355**, 1840.
20 P. P. Ghosh and A. R. Das, *J. Org. Chem*., 2013, **78**, 6170.
21 M. Sharma, S. Manohar and D. S. Rawat, *J. Heterocycl. Chem.*, 2012, **49**, 589.
22 U. C. Rajesh, J. Wang, S. Prescott, T. Tsuzuki and D. S. Rawat, *ACS Sustainable Chem. Eng*., 2015, **3**, 9.
23 K. Arya, D. S. Rawat and H. Sasai, *Green Chem.,* 2012, **14**, 1956.
24 U. C. Rajesh, Divya and D. S. Rawat, *RSC Adv*., 2014, **4**, 41323.
25 U. C. Rajesh, R. Kholiya, A. Thakur and D. S. Rawat, *Tetrahedron Lett*., 2015, **56**, 1790.
26 U. C. Rajesh, R. Kholiya, V. S. Pavan and D. S. Rawat, *Tetrahedron Lett*., 2014, **55**, 2977.

27 U. C. Rajesh, S. Manohar and D. S. Rawat, *Adv. Synth. Catal*., 2013, **355**, 3170.

28 K. Arya, U. C. Rajesh and D. S. Rawat, *Green Chem*., 2012, **14**, 3344.

29 A. Thakur, M. Tripathi, U. C. Rajesh and D. S. Rawat, *RSC Adv*., 2013, **3**, 18142.

30 Y. Gu, *Green Chem*., 2012, **14**, 2091.

31 M. Li, A. Taheri, M. Liu, S. Sun and Y. Gu, *Adv. Synth. Catal*., 2014, **356**, 537.

32 Y.Gao and D. M. Du, *Tetrahedron: Asymmetry*, 2013, **24**, 1312.

33 G. Shanthi, P. T. Perumal, U. Rao and P. K. Sehgal, *Indian J. Chem.* B, 2009, **48**, 1319.

34 L. Wang, M. Huang, X. Zhu and Y. Wan, *Appl. Catal*. A, 2013, **454**, 160.

35 V. Lucchini, M. Noe, M. Selva, M. Fabris and A. Perosa, *Chem. Commun*., 2012, **48**, 5178.

36 A. K. Chakraborti and S. R. Roy, *J. Am. Chem. Soc*., 2009, **131**, 6902

37 A. Zhu, R. Liu, L. Li, L. Li, L. Wang and J. Wang, *Catal. Today*, 2013, **200**, 17.

38 A. Alizadeh, M. M. Khodaei and A. Eshghi, *J. Org. Chem*., 2010, **75**, 8295.

39 K. Aggarwal, K. Vij and J. M. Khurana, *RSC Adv*., 2014, **4**, 13313.