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ARTICLE TYPE

Synthesis and evaluation of anticancer activity of novel andrographolide derivatives

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A series of 3,19-O-acetal derivatives of andrographolide 1 have been synthesized by protecting hydroxyls at C-3 and C-19 in a novel route. All the derivatives were evaluated for *in vitro* anticancer activity. Among the synthesized derivatives, compound 3, 3a, 3d, 3e, 7 and 8 showed potential cytotoxicity against human cancer cell lines A549 (lung), Hela (cervical), ACHN (renal), B-16 (melanoma) and IEC-6 (small intestine). Binding mode conformation was evaluated through docking simulations, while bioavailability/drug likeness was evaluated through predictive ADME screening studies. All the derivatives were characterized by spectroscopy and the stereo chemistry of compounds 3a and 3e were also confirmed by X-ray analysis.

Introduction

Andrographis paniculata Nees. (Family: Acanthaceae), commonly known as 'king of bitters,' is a well-known medicinal herb of India used in a variety of human illness.[1] Andrographolide **1** and 14-Deoxy-11,12-didehydroandrographolide **2** (Figure 1), are the two major bioactive constituents of this plant. Extracts of the plant and the major compounds have shown multiple pharmacological properties such as, antibacterial,[2] antimalerial,[3] immunostimulant,[4] anti-HIV,[5] anti-inflammatory,[6] antihepatotoxic,[7] antihyperglycaemic,[8] antimicrobial,[9] cardiovascular,[10] antidiabetic[11] and anticancer activities.[12] Structurally, compound **1** is a bicyclic diterpene with α-alkylidene γ-butyrolactone ring, two olefin bonds $\Delta^{8(17)}$, $\Delta^{12(13)}$, and three hydroxyls at C-3, C-14 (secondary) and C-19 (primary) respectively. Structure-Activity Relationship (SAR) studies of **1** showed that an intact γ-butyrolactone ring, double bonds at C-8, C-12 and hydroxyl at C-14 are important for cytotoxic activity. Substitution of acetyl functionality at C-14 hydroxyl as well as protection of C-3 and C-19 hydroxyls with aromatic aldehydes increased the cytotoxicity.[13-16] Also, the 15-alkyldene derivatives with protection of hydroxyls at C-3 and C-19 by aromatic aldehydes were reported as potent α-glucosidase inhibitors.[17, 18]

Andrographolide and its analogues promote apoptosis in human cancer cells by suppressing cell signalling pathways and regulating the expression of some pro-apoptotic markers. It was also reviewed that, andrographolide showed promising anticancer activity by downregulating tumor promoting factor, hypoxia-inducible factor-1a, and also one of the cell surface receptors EGFR in A549 cell line (Ref:19). Hence, multiple and versatile anticancer mechanisms of action made andrographolide and its analogues potential anticancer drug candidates.

In continuation to our earlier work on semi synthesis of natural bioactive molecules,[20] compounds **1** and **2** were isolated from *A. paniculata* as reported,[21] and designed a synthetic scheme to obtain novel alkoxy derivatives. To our surprise, when compound **1** reacted with ethanol in presence of Ceric Ammonium Nitrate (CAN), at ambient temperature, a cyclic acetal **3** was obtained instead of an ether formation without effecting 14-hydroxyl group, which is an important pharmacophore of andrographolide (Scheme 1).

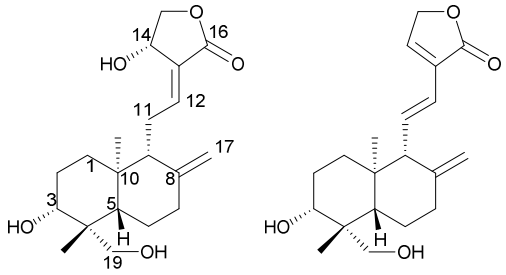


Figure 1. Structures of compounds isolated from *A.Paniculata.*

Acetals have been used as a common masking agents for 1,3-diols and is usually synthesized by treating with carbonyls in presence of acid catalysts (inorganic or organic), lewis acid with or without dehydrating agents.[22-27] Due to the greater stability of acetals to basic, nucleophilic and redox conditions, they are most commonly used as protecting groups for diols and carbonyl compounds in organic synthesis and for the generation of chiral auxiliaries for asymmetric induction.[28, 29] However, these synthetic approaches suffer harsh reaction conditions (strong acids, high temperatures), multiple products formation, tedious

procedures, expensive catalysts and chemicals harmful to the environment. Further, the acidic catalysts can lead to cleavage of other protecting groups and can undergo competitive reactions such as elimination (dehydration) or isomerization etc. Hence, there is a need to find out efficient catalysts which can selectively protect 1,3-diols, under mild reaction conditions, to generate more stable acetal derivatives of natural bioactive molecules like andrographolide **1**. Acetal derivatives of compound **1** were reported using direct condensation with aldehydes in presence of H_2SO_4, under reflux conditions.[18]

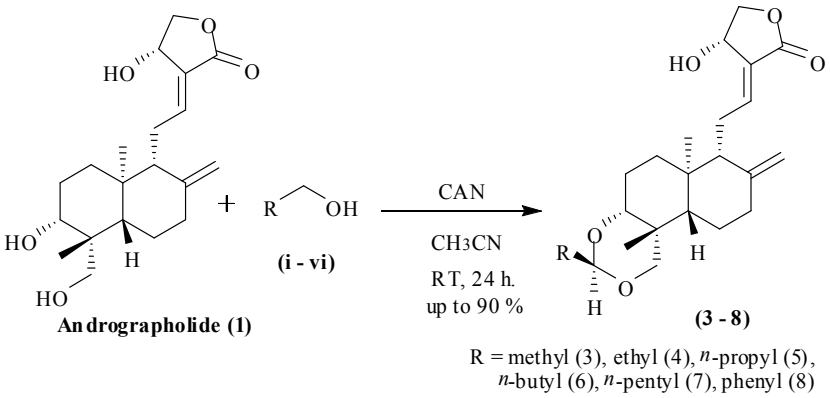
Hear, we disclose the role of CAN as a highly efficient catalyst in cyclic acetal formation, giving moderate to excellent yields in one pot from diols and alcohols, without resorting to prolonged reaction times, high temperatures, azeotropic removal of water etc. Besides being a one-electron oxidizing agent, CAN also act as either bronsted acid or as a lewis acid.[30-32]CAN is widely used in oxidation of alcohols,[33] cleavage of acetals and ketals,[34] formation of carbon-carbon[35, 36]or carbon-heteroatom bond,[36, 37] including etherification,[38] esterification,[39] 1,3-oxathioacetalisation[40] etc.

This paper reports the formation of cyclic acetals derivatives (**3-8**) of **1**, instead of simple ethers, when reacted with various primary alcohols in presence of CAN. All the derivatives were screened for *in vitro* anticancer activity against human cancer cell lines A549 (lung), HeLa (cervical), ACHN (renal cell carcinoma), B-16 (melanoma) and IEC-6 (small intestine). Binding mode conformation of the studied compounds was evaluated through molecular docking studies on receptor targets Epidermal Ggrowth Factor Receptor (EGFR) and α,β-tubulin. Oral bioavailability/drug likeness compliance of studied compounds was evaluated through predictive ADME (Absorption, Distribution, Metabolism, Excretion) screening.

Results and discussion

Chemistry

Compounds **3-8** were synthesized, in one pot, by protecting 1,3-diols (C-3 and C-19) of **1** with five equivalents of primary alcohols (**i-vi**) in presence of two equivalents of CAN in acetonitrile (Scheme 1) at ambient temperatures in quantitative yields (35-95%). CAN initially oxidizes alcohols to corresponding aldehydes which then leads to the formation of cyclic acetals by protecting 1,3-diols (Fig. 2). Acetonitrile was found to be the best solvent amongst water, acetone, chloroform and methanol. Increase in the reaction time and increase in the quantity of CAN did not show significant effect on the overall yield. As the carbon chain length of alcohols is increased, the yields of cyclic acetals decreased. Methanol, *iso*-propyl alcohol, *t*-butanol, cyclohexanol and phenol did not undergo this reaction, as they were unable to form corresponding aldehydes/ketones at above said conditions. Blank reaction of **1** with CAN did not show any conversion of C-3, C-14 and C-19 hydroxyls into respective aldehydes/ketones.



Scheme 1.Synthetic route for derivatives **3-8** from andrographolide **1**.

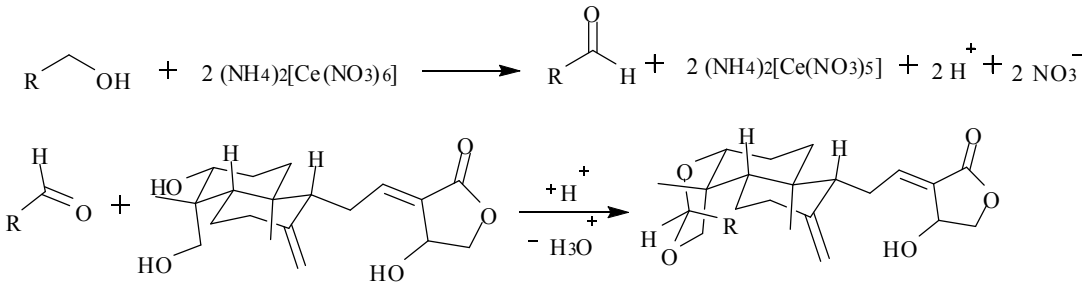
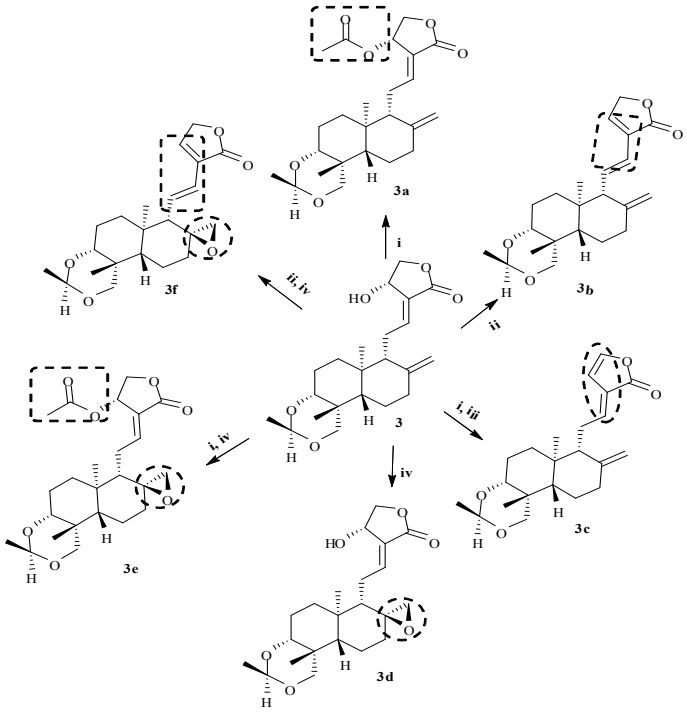


Figure 2.Proposed mechanism for Scheme 1.

Compound **3**, with an ethylidenyl moiety was further subjected to structural modifications (Scheme 2). In order to determine the role of C-14 hydroxyl towards cytotoxic activity, compound **3** was acetylated with Ac_2O/TEA in CH_2Cl_2 to yield **3a**, which

when treated with DMAP in CH_2Cl_2 yielded **3c** by loss of 14-hydroxyl as its acetate.[41] But when compound **3** was refluxed with Al_2O_3 in pyridine, dehydration product **3b** yielded.[42] To understand the role of the exocyclic double bond at C-8, compounds **3**, **3a** and **3b** were treated with *m*-CPBA in CH_2Cl_2 to obtain epoxides **3d**, **3e** and **3f** respectively.

Structures of all analogues were elucidated by various spectroscopy experiments like ^1H&^{13}C-NMR, Mass and IR etc. Further, the stereochemistry of compounds **3a** and **3e** were confirmed by single crystal X-ray diffraction studies (Figure 3). The absolute stereochemistry at C-3, C-4, C-5, C-8, C-9, C-10 and C-14 was assumed to be the same as that reported in **1**.[17,21] Based on this crystallographic information, the stereo centre at acetal ring is confirmed as (*R*) configuration.



Scheme 2. Synthesis of compounds**3a-f** from compound **3**.Reagents and conditions: (i) Ac_2O/TEA, CH_2Cl_2, rt, 30 min, 95 % yield; (ii) Al_2O_3, dry pyridine, reflux, 12 h, 90 % yield; (iii) DMAP, CH_2Cl_2, rt, 1 hr, 72 % yield; (iv) *m*-CPBA, CH_2Cl_2, rt, 4 h, 65-70 % yields.

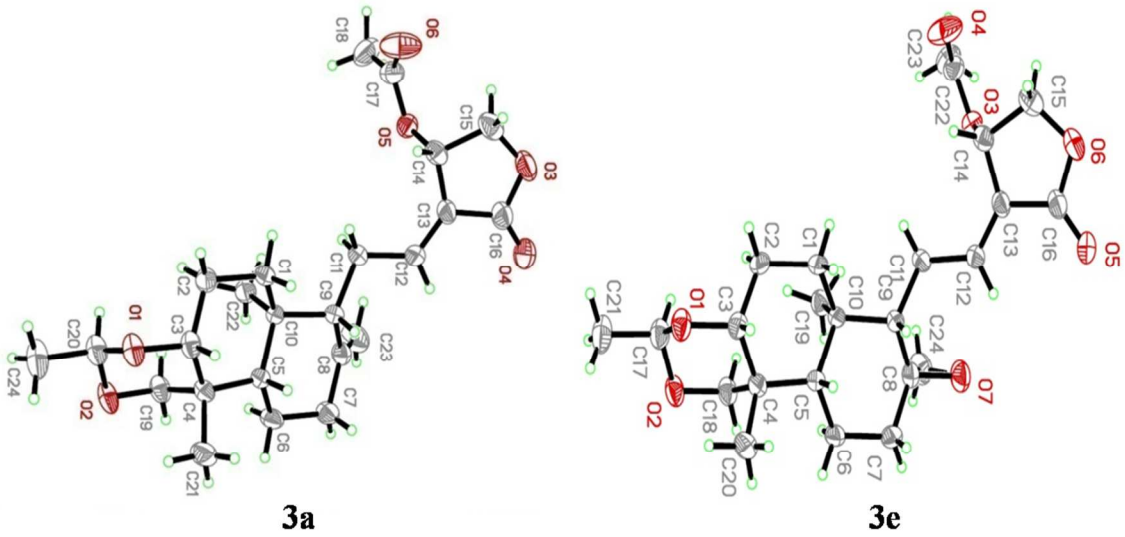


Figure 3. Single X-ray crystal structures (ORTEP drawing) of compounds**3a** and **3e**with thermal displacement ellipsoids drawn at 30%probability.

Compounds **3-8** including **3a-3f** were evaluated for *in vitro* cytotoxic activity against five human cancer cell lines A549 (lung), HeLa (cervical), ACHN (renal cell carcinoma), B-16 (melanoma) and IEC-6 (small intestine) by MTT assay.[43] Table 1 reveals that the 3,19-O-ethylidene andrographolide **3** was four fold potentially cytotoxic against A549 (IC_{50} 2.43 µg/mL) and two fold potential against HeLa (IC_{50} 4.27 µg/mL) cell lines when compared to parent **1**. As the length of the aliphatic carbon chin increased on acetal functionality from ethylidene to *n*-pentylidene **3-6** cytotoxicity was decreased in almost all the cell lines.

Further, the benzylidene acetal derivative **8** was twofold cytotoxic when compared to **1** in HeLa (IC_{50} 3.80 µg/mL) and A549 (IC_{50} 4.07 µg/mL) cell lines. Acetylation of 14-hydroxyl of **3 (3a)** did not significantly affected the cytotoxicity potential except in case of ACHN cell line. The dehydration of **3** resulted in positional isomers **3b** and **3c**, were inactive in all the cell lines. Epoxidation of **3**, **3a**, **3b** resulted in **3d**, **3e**, **3f** were either retained or decreased their cytotoxicity potential.

In conclusion, these results indicate that the protection of 3,19-hydorxyl groups of Andrographolide with suitable ethylidene/benzylidene moiety induced significant cytotoxicity. Either acetylating or dehydrating the 14-hydroxtyl of lead compound **3** affected its cytotoxic effect in all the cell lines. Epoxidation of **3** at C-8 position did not impart any significant change on its overall cytotoxicity.

Table 1.*In vitro*anticancer activity of andrographolide derivatives against human cancer cell lines

Compound	Cell growth inhibition in IC_{50} (µg/mL) [a]				
	HeLa	IEC-6	ACHN	B-16	A549
1	10.42	8.26	3.03	7.54	9.71
2	149.09	169.36	327.77	25.17	117.40
3	4.27	6.34	2.47	4.78	2.43
4	8.91	14.21	14.68	10.23	8.12
5	27.03	14.14	32.91	44.35	22.98
6	14.07	31.21	15.35	21.09	33.53
7	8.51	22.37	9.54	10.0	7.07
8	3.80	19.23	4.78	9.54	4.07
3a	4.43	7.23	8.54	4.01	3.34
3b	56.21	94.3	125.23	62.01	88.71
3c	48.56	39.98	60.65	43.0	46.87
3d	6.97	8.76	4.49	6.34	4.34
3e	7.12	14.51	5.58	6.98	4.37
3f	7.78	35.06	57.34	44.07	18.21
Doxorubicin	1.28	2.60	2.08	3.16	3.2

[a] Data represents mean value of two independent determinations.

Molecular docking

The aim of the molecular docking study was to elucidate whether the synthesized derivatives modulates the activity of human anticancer targets, epidermal growth factor receptor (EGFR) and α,β-tubulin and also to identify the molecular mechanism of action. Due to the availability of X-ray 3D-crystallographic protein structures of cervical cancer (HeLa cell) derived alpha beta-tubulin dimer (α,β-tubulin) at 3.5Å resolution (PDB: 1JFF)[44] and lung cancer (A549 cell) derived EGFR at 2.88Å resolution (PDB: 2ITW)[45], molecular docking study was performed to explore the mechanism of action of studied active andrographolide derivatives. Anticancer active compounds were docked on EGFR kinase domain and explored the orientation and binding site residues. When compared to the docking score of standard drug doxorubicin (total score 4.9812), except compound **3e** (total score 4.7946), docking results of compounds **3, 3a, 3d,** and **7** on EGFR kinase domain showed high binding affinity with total scores of 5.3004, 5.7828, 5.0596, and 5.3047 respectively (Suppl. Table 2) (Figure 4). Moreover, compound **3** showed hydrogen (H-) bonds with amino acid residues THR-854 and ASP-855, **3a** with THR-854, **3d** with THR-854, THR-790 and MET-793 and **3e** with GLY-144 and LYS-254 respectively. Here the identified interacting binding site residue THR-854 is also be reported as a 'gatekeeper' residue of EGFR kinase domain[45].

Similarly, in comparison to control drug doxorubicin (total score 4.6952), docking results of compounds **1**, **3a**, **3e** and **7** against α,β-tubulin dimer protein showed higher binding affinity with total scores of 8.9906, 4.7654, 4.7946 and 5.2077, respectively (Suppl. Table 3) (Figure 5). Moreover, compound **1** showed H-bonds with binding site residues ALA-174, GLY-142, ILE-171, GLY-146 and GLN-11, while compound **3a** showed H-bonds with binding site residues ALA-12, LYS-254 and GLY-146. Similarly, compound **3e** showed H-bonds with GLY-144 and LYS-254 and compound **7** showed an H-bond with VAL-177.

Pharmacokinetic parameters compliance

The pharmacokinetics parameters such as ADME are important descriptors for human therapeutic use of any compound. These ADME descriptors were calculated and checked for compliance with their standard ranges. Screening for active and ADME compliant 3,19-O-acetal derivatives of andrographolide namely, compounds **1, 3, 3a, 3d, 3e, 7,** and **8** were evaluated through its calculated logP (octanol–water partition coefficient), which has been implicated in logBB (blood–brain barrier) penetration and permeability studies. The logP descriptor used to correlate passive molecular transport through membranes. All derivatives showed compliance with standard range of Lipinski's rule of five[46] for oral bioavailability. The distribution of each derivative in human was evaluated by following calculated descriptors e.g., logBB, permeability (apparent Caco-2 (a human colon carcinoma cell line) and MDCK (Madin-Darby canine kidney cell line) permeability, logKp for skin permeability), which also showed compliance with standard cut-off range of 95% of known drugs (Qikprop, Schrödinger, USA). The volume of distribution and plasma protein binding refer by logKhsa. The process of excretion, which eliminates the compound from the human body, evaluated by molecular weight and calculated logP. The calculated values of these ADME parameters showed close similarity with that of standard drug doxorubicin and lies within the standard range of values exhibited by 95% of all known drugs (Suppl. Table 4).

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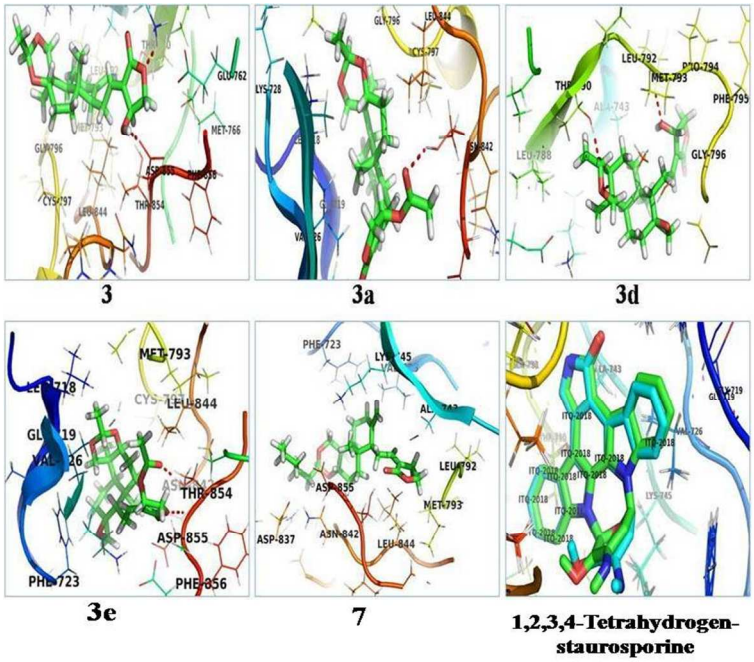

Figure 4. Compounds **3**, **3a**, **3d**, **3e**, and **7**docked on anticancer target EGFR (PDB ID: 21TW) revealing respective binding site residues. The co-crystallized inhibitor 1,2,3,4-tetrahydrogen staurosporine re-docked on EGFR (PDB: 21TW) with 0.6245 Å of RMSD (root mean square deviation).

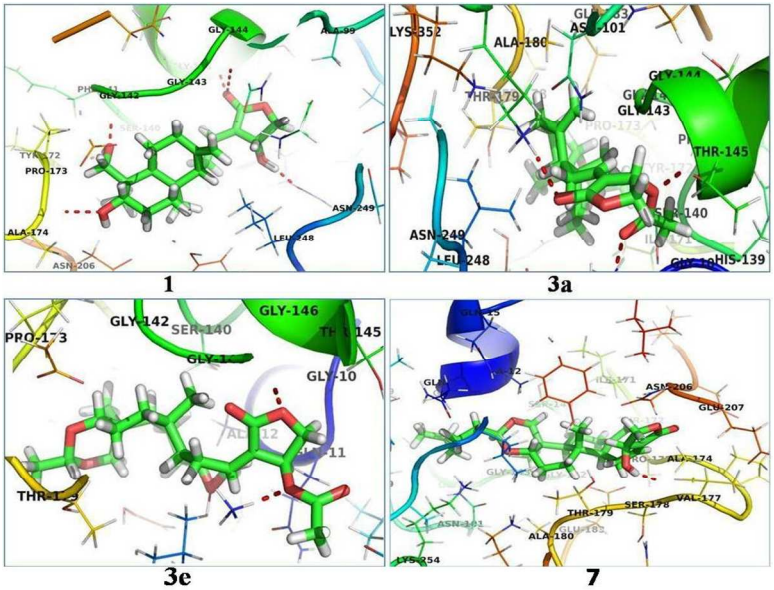

Figure 5. Compound **1**, **3a**, **3e**, and **7** docked on anticancer target α,β-tubulin (PDB ID: 1FF) revealing respective binding site residues.

Methodology

Molecular docking parameters

To find the possible interactions of derivatives of compound **1**, we docked all compounds on known human anticancer targets αβ-tubulin and epidermal growth factor receptor (EGFR). Sybyl X v2.0 molecular modeling software (Tripos/Certara, USA) interfaced with Surflex-Dock module was used for molecular docking studies. Program automatically docks ligand into binding pocket of a target protein by using protomol based algorithm and empirically produced scoring function. The X-ray crystallographic structures of αβ-tubulin complex (PDB: 1JFF)[44] and EGFR complex (PDB: 2ITW)[45] were retrieved from the protein databank (PDB; www.rcsb.org) and modified for docking calculations. Protein structure minimization was performed by applying Tripos force field and partial atomic charges were calculated by Gasteiger-Huckel method. In reasonable binding pocket, all the compounds were docked into the binding pocket and 20 possible active docking conformations with different scores were obtained for each compound. During the docking process, all of the other parameters were assigned to their default values[46]. Calculations of ADME properties of studied derivatives were calculated through trial license of QikProp software (Schrödinger, USA).

Conclusions

Developing promising anticancer agents by synthesis of 3,19-O-acetal derivatives (**3-8**) of andrographolide with alcohols in presence of CAN in one pot, is a novel method. Compounds **3**, **4**, and **7** are structurally novel and compounds **3**, **7** and **8** showed promising cytotoxic activities, in *in vitro* mode, compared to the parent **1**. Potent anticancer active compound **3** was further derivatized to **3a-3f** to explore Structure Activity Relationship. It was found that by inducing cyclic acetal protection at C-3 and C-19 or ester at C-14 and or both, enhances the anticancer activitybut removing the C-14 hydroxyl reduces the cytotoxicity. Binding affinity of studied derivatives revealed on known anticancer targets EGFR and α, β-tubulin through docking. All compounds showed compliance with standard range of known drug's ADME parameters.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data of all compounds, X-ray crystallographic data for **3a**, **3e** (CCDC numbers 937572, 943354). See DOI: 10.1039/b000000x/

1. R. N. Chopra, S. L. Nayar and I. C. Chopra, in Glossary of Indian Medicinal Plants, Council for Scientific and Industrial Research, New Delhi, 1956, pp 18.
2. S. Gupta, M.A. Choudhry, J.N.S. Yadava, V. Srivastava and J.S. Tandon,*Int. J. Crude Drug Res.*,1990,**28**, 273–283.
3. N.A.R.N. Najib, T. Furuta, S. Kojima, K. Takane and M.M. Ali, *J. Ethnopharmocol.*,1999,**64**, 249–254.
4. A. Puri, A. Saxena, R. P. Saxena, K. C. Saxena, V. Srivastava and J. S. Tandon, *J. Nat. Prod.*, 1993, **56**, 995–999.
5. A. Basak, S. Cooper, A. G. Roberge, U. K. Banik, M. Chretien and N. G. Seidah, *Biochem. J.*, 1999, **338**, 107–113.
6. S. Madav, S. K. Tanda, J. Lal and H. C. Tripathi, *Fitoterapia*, 1996, **67**, 452–458.
7. B. Saraswat, P. K. S. Visen, G. K. Patnaik and B. N. Dhawan, *Fitoterapia*, 1995, **66**, 415–420.
8. B. C. Yu, C. R. Hung, W. C. Chen and J. T. Cheng, *Planta Med.*, 2003, **69**, 1075–1079.
9. Z. J. Shao, X. W. Zheng, T. Feng, J. Huang, J. Chen, Y. Y. Wu, L. M. Zhou, W. W. Tu and H. Li, *Can. J. Physiol. Pharmacol.*, 2012, **90**, 647–653.
10. A. Y. Woo, M. M. Waye, S. K. Tsui, S. T. Yeung and C. H. Cheng, *J. Pharmacol. Exp. Ther.*, 2008, **325**, 226–235.
11. J. Lal, H. C. Tripathi and S. K. Tandon, *Indian J. Pharmacol.*, 1986, **18**, 58–61.
12. S. Rajagopal, R. A. Kumar, D. S. Deevi, C. Satyanarayana and R. Rajagopalan, *J. Exp. Ther. Oncol.*, 2003, **3**, 147–158.
13. S. Nanduri, V. K. Nyavanandi, S. S. R. Thunuguntla, S. Kasu, M. K. Pallerla, P. S. Ram, S. Rajagopal, R. A. Kumar, R. Ramanujam, J. M. Babu, K. Vyas, A. S. Devi, G. O. Reddy and V. Akella, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4711–4717.
14. S. R. Jada, G. S. Subur, C. Matthews, A. S. Hamzah, N. H. Lajis, M. S. Saad, M. F. G. Stevens and J. Stanslas, *Phytochemistry*, 2007, **68**, 904–912.
15. S. R. Jada, C. Matthews, M. S. Saad, A. S. Hamzah, N. H. Lajis, M. F. G. Stevens and J. Stanslas, *Br. J. Pharmacol.*, 2008, **155**, 641–654.
16. S. R. Jada, A. S. Hamzah, N. H. Lajis, M. S. Saad, M. F. G. Stevens and J. Stanslas, *J. Enzyme Inhib. Med. Chem.*, 2006, **21**, 145–155.
17. H.- W. Xu, G. -F. Dai, G. -Z. Liu, J. -F. Wang and H. -M. Liu, *Bioorg. Med. Chem.*, 2007, **15**,4247–4255.
18. G. -F. Dai, H. -W. Xu, J. -F. Wang, F. -W. Liu and H. -M. Liu, *Bioorg. Med. Chem. Lett.*, 2006,**16**, 2710–2713.
19. J. C. W. Lim, T. K. Chan, D. SW. Ng, S. R. Sagineedu, J. Stanslas and WS. F. Wong, Clin. Exp. Pharmacol. Physiol., 2012, **39**, 300–310.
20. D. Ponnam, S. Shilpi, K. Srinivas, L. Suiab, S. Alam, Z. Amtul, N. K. Arigari, K. K. Jonnala, L. Siddiqui, V. Dubey, A. K. Tiwari, S. Balasubramanian and F. Khan, *Eur. J. Med. Chem.*, 2014, **87**, 735-744.
21. T. Fujita, R. Fujitani, Y. Takeda, Y. Takaishi, T. Yamada, M. Kido and I. Miura, *Chem. Pharm. Bull.*, 1984, **32**, 2117–2125.
22. T. W. Greene and P. G. M. Wuts, in Protective Groups in Organic Synthesis, Wiley, New York, 3rd eds., 1999, chapter 2, pp. 201–245.
23. P. J. Kocienski, in Protecting Groups, Thieme, Stuttgart, 3rd edn., 1994.
24. C. B. Reese, in Protective Group in Organic Chemistry, ed. J. F. W. McOmie, Plenum Press, London, 1973, pp. 95–143.
25. D. Seebach, R. Imwinkelried and T. Weber, in Modern Synthetic Methods 1986, ed. R. Scheffold, Springer Verlog, Berlin, 1986, Vol. 4, pp. 125–259.
26. F. A. J. Meskens, *Synthesis*, 1981, **7**, 501–522.

27. M. Schelhaas and H. Waldmann, *Angew. Chem. Int. Ed. Engl.*,1996,**35**, 2056–2083.
28. J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581–1590.
29. A. Alexakis and P. Mangeney, *Tetrahedron: Asymmetry*, 1990, **1**, 477–511.
30. V. Nair and A. Deepthi, *Chem. Rev.*, 2007, **107**, 1862–1891.
31. V. Sridharan and J. C. Menendez, *Chem. Rev.*, 2010, **110**, 3805–3849.
32. J. R. Hwu and K. Y. King, *Curr. Sci.*, 2001, **81**, 1043–1053.
33. Y. Hatanaka, T. Imamoto and M. Yokoyama, *Tetrahedron Lett.*, 1983, **24**, 2399–2340.
34. I. E. Markó, A. Ates, A. Gautier, B. Leory, J. -M. Plancher, Y. Quesnel and J. -C. Vanherk, *Angew. Chem., Int., Ed.*, 1999, **38**, 3207–3209.
35. V. Nair, J. Mathew and J. Prabhakaran, *Chem. Soc. Rev.,* 1997, **26**, 127–132.
36. V. Nair, L. Balagopal, R. Rajan and J. Mathew, *Acc. Chem. Res.*, 2004, **37**, 21–30.
37. V. Nair, S. B. Panicker, L. G. Nair, T. G. George and A. Augustine, *Synlett.,*2003, **2**, 156–165.
38. N. Irranpoor and E. Mothaghineghad, *Tetrahedron*, 1994, **50**, 1859–1870.
39. W. -B. Pan, F. -R. Chang, L. -M. Wei, M. -J. Wu and Y. -C. Wu, *Tetrahedron Lett.*, 2003, **44**, 331–334.
40. G. Maiti and S. C. Roy, *Syn. Commun.*, 2002, **32**, 2269–2273.
41. S. Nanduri, V. K. Nyavanandi, S. S. R. Thunuguntla, M. Velisoju, S. Kasu, S. Rajagopal, R. A. Kumar, R. Rajagopalan and J. Iqbal, *Tetrahedron Lett.*, 2004, **45**, 4883–4886.
42. H. -W. Xu, J. Zhang, H. -M. Liu and J. -F. Wang, *Synth. Commun.*, 2006, **36**, 407–414.
43. A. Kamal, G. Ramakrishna, P. Raju, A. V. S. Rao, A. Viswanath, V. L. Nayak and S. Ramakrishna, *Eur. J. Med. Chem.*, 2011, **46**, 2427–2435.
44. S. Bhattacharya, N. M. Kumar, A. Ganguli, M. P. Tantak, D. Kumar and G. Chakrabarti, *PLoS One*, 2013, 8, e76286.
45. C.H. Yun, T.J. Boggon, Y. Li, M.S. Woo, H. Greulich, M. Meyerson and M.J. Eck, *Cancer Cell,* 2007, **11**, 217–227.
46. D.K. Yadav, K. Kalani, A.K. Singh, F. Khan, S.K. Srivastava, A.B. Pant. *Curr Med Chem.* 2014, 21(9):1160-70.