RESEARCH ARTICLE

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2017, 8, 176**Design, synthesis, anticancer activity and docking studies of theophylline containing 1,2,3-triazoles with variant amide derivatives†‡**Radhakrishnam Raju Ruddaraju,^a Adharvana Chari Murugulla,^{*a} Ravindar Kotla,^a Muni Chandra Babu Tirumalasetty,^b Rajendra Wudayagiri,^b Shobha Donthabakthuni^a and Ravichandar Maroju^c

A new series of theophylline analogues containing 1,2,3-triazoles with different amide groups (22–41) has been designed and synthesized, and their biological activities have been evaluated as potential anticancer agents. The anticancer activities of the synthesized compounds were studied in four cancer cell lines viz. lung (A549), colon (HT-29), breast (MCF-7) and melanoma (A375). Furthermore, these compounds were screened for computational ADME and Lipinski's analysis followed by molecular docking and binding energy calculations against the various therapeutic targets involved in cell proliferation. The *in vitro* results demonstrate that compounds 22, 27, 36 and 40 have pivotal anticancer activity. Among these, compounds 22 and 27 have significant cytotoxic activity in all three cell lines; the *in silico* docking studies also reveal that compounds 22, 27 and 36 have good dock scores, binding affinities and binding energies towards human epidermal growth factor receptor 2. This is the first report to demonstrate theophylline hybrids containing 1,2,3-triazoles as potential anticancer agents.

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www.rsc.org/medchemcomm**Introduction**

Cancer is considered as the second most lethal disease; it is responsible for 21% of annual deaths globally.¹ Approximately 7.6 million people die of cancer every year worldwide, which is expected to reach 13 million in 2030. As per a report published in *The Lancet*,² the total deaths due to cancer in India were 0.55 million in 2010. Lung, breast, colon and melanoma cancers are the most common cancers in the developing and underdeveloped countries. Lung and breast cancers among men and women are more prevalent in the developed countries. Overall, 16.8% of people in the United States diagnosed with lung cancer survive five years after the diagnosis.³ Whereas the breast cancer survival rates in the developed world are high;⁴ 80% to 90% of patients in England and in the United States live for at least 5 years after diagnosis.^{5,6}

However, globally, colon cancer is the third most common type of cancer, comprising about 10% of all cases.⁷ It is less common in women than in men and in developed countries. Melanoma is the most dangerous type of skin cancer. It is more common in men than in women.⁸ Globally, in 2012, it occurred in 2.32 lakhs people and resulted in 55 000 deaths. For this purpose, chemotherapy is the most commonly used treatment worldwide.⁹ However, it has several serious side effects and drawbacks. Thus, these limitations compelled us to search for novel anticancer agents with diverse chemical structures; herein, we report the synthesis and biological evolution of theophylline containing 1,2,3-triazoles with different amide derivatives as potential anticancer agents.

Analogues of naturally occurring purine bases are valuable tools in defining the chemical interactions involved in a specific biological response. Structural alterations of xanthine have resulted in several potent biological systems *e.g.* theophylline, also known as 1,3-dimethylxanthine, is a proven bronchodilator drug used in the therapy for respiratory diseases such as asthma or chronic pulmonary obstructive disease (COPD).^{10–12} Theophylline derivatives with alterations at their 7- and 8-positions have been investigated with respect to their bronchospasmolytic,^{13–16} anticancer¹⁷ and circulatory blood system activities.¹⁸ The aim of this study is to expand the pharmacological profile of theophylline to reduce its side effects and to identify possible candidates for further development.

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Meanwhile, 1,2,3-triazoles have gained enormous attention in recent years owing to their broad spectrum of pharmaceutical activities and their highly diverse biological activities, such as anticancer,^{19–21} antifungal, antibacterial,^{22–24} antituberculosis^{25–27} and antiviral.^{28–30} Thus, click chemistry has attracted extensive interest in almost all aspects of drug discovery, such as lead discovery through combinatorial chemistry, target-templated *in vitro* chemistry, proteomics, and DNA research using bio-conjugation reactions. Bioactive theophylline and 1,2,3-triazole molecules are shown in Fig. 1.

Based on their biological significance, the integration of theophylline and 1,2,3-triazole pharmacophore units with amide linkages in one molecular platform has been envisaged to generate new theophylline derivatives containing 1,2,3-triazoles with a variant amide analogue hybrid framework with anticancer activity. In addition, structure–activity relationship (SAR) studies, molecular docking, and toxicity screening were performed, and the ADME properties of the compounds were evaluated (Fig. 2).

Results and discussion

Chemistry

Different commercially available aryl halide compounds, 4, 6, 9, 11 and 13, were treated with boronic acids or boronate esters 3, 8 and 14 using potassium phosphate as a base and Pd(dppf)Cl₂·CH₂Cl₂ as a catalyst in 1,4-dioxane and water at 100 °C for 10 to 16 hours; this gave biphenyl amine compounds 5, 7, 10, 12 and 15, as shown in Scheme 1.

The synthesis of theophylline containing 1,2,3-triazoles with different aliphatic cyclic amides and biphenyl amide analogues (compounds 22 to 41) is outlined in Scheme 2. Initially, the commercially available starting material theophylline 16 was alkylated with ethyl 2-bromoacetate and K₂CO₃ in *N,N*-dimethylformamide (DMF) at 85 °C for 12 hours, which gave 17a in 84% yield; in contrast, 17b was prepared by a Mitsunobu reaction. Theophylline 16 was reacted with ethyl 2-hydroxypropanoate using triphenylphosphine (TPP) and

diisopropyl azodicarboxylate (DIAD) at room temperature, affording 17b in 50% yield. The ester compounds 17a and 17b were hydrolyzed with LiOH·H₂O in THF and H₂O at room temperature for 2 hours to afford 18a and 18b in 91% and 98% yield, respectively. The propynyl compounds were prepared by coupling acid compounds 18a and 18b with propargyl alcohol using *N,N*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) at room temperature for 16 hours; this gave 19a and 19b in 78% and 83% yield, respectively. Lastly, the 1,2,3-triazole ring was constructed based on Cu(I)-catalyzed 1,3-dipolar cycloaddition between the appropriate alkyne and azide as the key step. The 1,2,3-triazoles were synthesized by reacting propynyl compounds 19a and 19b with 3-azidopropanoic acid in the presence of CuSO₄·5H₂O and sodium ascorbate in *t*-BuOH and H₂O for 16 hours; this gave 20a and 20b in 85% and 78% yield, respectively, whereas 2-azido acetic acid in the presence of CuSO₄·5H₂O and sodium ascorbate in *t*-BuOH and H₂O for 16 hours gave 21a and 21b in 82% and 77% yield, respectively.

Finally, the 1,2,3-triazole acid compounds 20a and 20b or 21a and 21b were coupled with different aliphatic cyclic amines or biphenyl amines using 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) and *N,N*-diisopropylethylamine (DIPEA) as a base in dichloromethane to afford the final compounds 22–41 in 44% to 86% yield.

Biological activity

Anticancer activity. The synthesized compounds were evaluated for their anticancer activities in four human cancer cell lines: lung (A549), colon (HT-29), breast (MCF-7) and melanoma (A375) (Tables 1 and 2). Interesting results were observed; the highest activities in lung cancer cells were displayed by compounds 27, 40 and 22 (IC₅₀ = 1.21 ± 0.16, 1.34 ± 0.14, and 1.40 ± 0.09 μM, respectively). The next molecule in this series, compound 32, also exhibited relatively high activity (IC₅₀ = 2.12 ± 0.26 μM); compounds 28 and 39 were also found to be active (IC₅₀ = 3.54 ± 0.44 and 4.20 ± 0.18 μM, respectively) compared to the remaining compounds, which proved to be inactive in lung cancer cells. The highest activity in colon cancer cells was again displayed by compound 27 (IC₅₀ = 2.30 ± 0.16 μM); compounds 36 and 39 (IC₅₀ = 2.90 ± 0.73 and 2.96 ± 0.10 μM) also exhibited good activities. The highest activities in the breast cancer cell line were demonstrated by compounds 22 and 27 (IC₅₀ = 2.20 ± 0.32 and 2.31 ± 0.41 μM, respectively). In this series, compounds 34 and 36 (IC₅₀ = 2.40 ± 0.17 and 2.71 ± 0.44 μM, respectively) also showed good activity compared to compounds 39, 37 and 28. Similarly, the highest activity in melanoma cancer cell lines was shown by compounds 22 and 35 (IC₅₀ = 2.51 ± 0.58 and 2.80 ± 0.29 μM, respectively). These results clearly indicated that compounds 22 and 27 were the most potent in all investigated cancer cell lines (lung, colon, breast and melanoma).

With regard to the amide analogues (22–31), the series of aliphatic cyclic amides showed massive differences in

Fig. 1 Bioactive theophylline and 1,2,3-triazole moieties.

A

B

Fig. 2 Molecular and LIGPLOT interactions of compounds 22 (A) and 41 (B) with the tyrosine kinase domain of human epidermal growth factor receptor 2 (HER2).

potency and selectivity with decreasing cyclic ring size. Here, a slight difference in two series of compounds, 22–25 and

26–30, which contain a methyl group on the α -carbon at position 7 of the theophylline ring, resulted in a dramatic change in activity. Among these, compounds 22 and 27 showed the highest anticancer activity against three cancer cell lines, *i.e.* lung, breast, melanoma for 22 ($IC_{50} = 1.40 \pm 0.09$, 2.20 ± 0.32 , and $2.51 \pm 0.58 \mu M$, respectively) and lung, colon, breast for 27 ($IC_{50} = 1.21 \pm 0.16$, 2.30 ± 0.16 , and $2.31 \pm 0.41 \mu M$, respectively) compared to the other compounds. In comparison, compound 22, in which the cyclohexyl ring was replaced with cyclopentyl and cyclobutyl rings to form compounds 23 and 24, respectively, displayed less activity against the four cancer cell lines. Similarly, compounds 26, 28 and 29, which contain cyclohexyl, cyclobutyl and cyclopropyl rings, displayed less activity against the four cancer cell lines than compound 27. Here, the anticancer activity of the cyclic amides 22–24 and 27–29 clearly showed a decreasing trend with decreasing ring size, as displayed by their losses of activity. Meanwhile, the other cyclic amides, such as the morpholine analogues in 25 and 30 and the ethyl piperazine derivative in 31, showed no improvement in potency or selectivity.

Scheme 1 Synthesis of biphenyl amine compounds 5, 7, 12 and 15. Reagents and conditions: (a) K_3PO_4 , $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, 1,4-dioxane: H_2O , $100^\circ C$, 10–16 h.

Scheme 2 Synthesis of aliphatic cyclic amide and biphenyl amide compounds **22–31** and **32–41**. Reagents and conditions: (a) (i) K₂CO₃, DMF, 85 °C, 12 h; (ii) TPP, DIAD, THF, rt, 5 h; (b) LiOH·H₂O, THF:H₂O, rt, 2 h; (c) DCC, DMAP, DCM, rt, 16 h; (d and e) CuSO₄·5H₂O, sodium ascorbate, *t*-BuOH:H₂O, rt, 16 h; (f, g and h) HATU, DIPEA, DCM, rt, 16 h.

Table 1 Anticancer activities (IC₅₀) of aliphatic cyclic amide analogues (**22–31**)

Compound						
R ₁	R ₂	No.	A549 (lung)	HT-29 (colon)	MCF-7 (breast)	A375 (melanoma)
H	Cyclohexyl	22	1.40 ± 0.09	52.3 ± 1.20	2.20 ± 0.32	2.51 ± 0.58
H	Cyclopentyl	23	4.70 ± 0.14	15.4 ± 1.29	12.8 ± 0.33	60.8 ± 4.61
H	Cyclobutyl	24	5.24 ± 0.49	19.2 ± 2.81	9.18 ± 0.99	61.2 ± 3.51
H	Morpholine	25	7.24 ± 1.02	38.2 ± 3.22	18.2 ± 1.81	58.2 ± 1.90
CH ₃	Cyclohexyl	26	34.6 ± 2.49	21.4 ± 0.60	7.54 ± 1.36	3.92 ± 0.59
CH ₃	Cyclopentyl	27	1.21 ± 0.16	2.30 ± 0.16	2.31 ± 0.41	63.2 ± 2.30
CH ₃	Cyclobutyl	28	3.54 ± 0.44	55.2 ± 2.76	6.33 ± 1.06	8.52 ± 0.34
CH ₃	Cyclopropyl	29	10.2 ± 0.68	14.8 ± 0.34	16.8 ± 0.85	68.2 ± 2.71
CH ₃	Morpholine	30	5.82 ± 0.39	6.2 ± 0.59	5.92 ± 0.30	24.8 ± 1.83
CH ₃	<i>N</i> -Ethylpiperazine	31	6.82 ± 0.41	24.2 ± 1.94	38.2 ± 2.62	62.3 ± 4.30
Combretastatin-A4			0.11 ± 0.19	0.93 ± 0.82	0.18 ± 0.5	0.21 ± 0.62

All assays were performed in triplicate; IC₅₀ values are reported as mean ± SD.

In the next series of compounds, substituting the aliphatic cyclic amide moiety with biphenyl amide structures, such as those found in **32–38**, typically resulted in less anticancer activity compared with the cyclic amide analogues. Meanwhile, some of the biphenyl series (**32–38**) still displayed good inhibition activities and showed values comparable to some of the better amide analogues; the reason for this is unclear. Compounds **32**, **34**, **35** and **36** showed higher anticancer activities than compounds **33**, **37** and **38**. A vital comparison between the two series of compounds, **32–34** and **35–37**, with

α -carbons at position 7 of the theophylline ring, displayed a change in activity. Comparing compounds **32** and **35**, both of which contain 2,3-bipyridine, **32** showed activity in the lung cell line (IC₅₀ = 2.12 ± 0.26 μ M) and **35** showed anti-melanoma activity (IC₅₀ = 2.80 ± 0.29 μ M); both compounds were inactive against the remaining three cell lines. Similarly, among compounds **33** and **36**, containing 2-phenylpyridine, and **34** and **37**, containing 3-phenylpyridine, compounds **33** and **37** showed no activity in all four cancer cell lines, whereas compounds **34** and **36**, interestingly, showed activity

Table 2 Anticancer activities (IC_{50}) of biphenyl amide analogues (32–41)

Compound						
R_1	R_4	No.	A549 (lung)	HT-29 (colon)	MCF-7 (breast)	A375 (melanoma)
H		32	2.12 ± 0.26	54.3 ± 2.10	53.8 ± 3.5	3.80 ± 0.31
H		33	4.70 ± 0.35	56.8 ± 2.36	8.41 ± 0.63	9.34 ± 0.55
H		34	53.4 ± 2.02	17.3 ± 0.43	2.40 ± 0.17	3.62 ± 0.34
CH_3		35	6.33 ± 0.18	50.2 ± 0.90	62.8 ± 3.27	2.80 ± 0.29
CH_3		36	4.90 ± 0.09	2.90 ± 0.73	2.71 ± 0.44	58.2 ± 1.58
CH_3		37	48.2 ± 0.26	27.5 ± 2.06	5.91 ± 0.28	10.31 ± 0.25
CH_3		38	6.82 ± 0.12	5.82 ± 0.46	18.4 ± 0.51	50.4 ± 3.41

R_1	R_3	No.	A549 (lung)	HT-29 (colon)	MCF-7 (breast)	A375 (melanoma)
H		39	4.20 ± 0.18	2.96 ± 0.10	5.72 ± 0.54	61.4 ± 2.56
H		40	1.34 ± 0.14	11.7 ± 0.19	13.5 ± 0.49	48.2 ± 2.86
CH_3		41	8.24 ± 0.05	7.23 ± 0.5	10.2 ± 0.31	63.4 ± 2.8
Combretastatin-A4			0.11 ± 0.19	0.93 ± 0.82	0.18 ± 0.5	0.21 ± 0.62

All assays were performed in triplicate; IC_{50} values are reported as mean $\pm$ SD.

in the breast and colon cancer cell lines; 34 was active against breast cancer ($IC_{50} = 2.40 \pm 0.17 \mu M$), while 36 was active against colon and breast cancer ($IC_{50} = 2.90 \pm 0.73$ and $2.71 \pm 0.44 \mu M$, respectively).

Other synthesized biphenyl amide analogues (*i.e.*, 39–41) were based on the aliphatic cyclic amide scaffold, which has been shown to display promising anticancer activity and selectivity. Compound 40 was shown to have slightly better anticancer activity towards lung cancer ($IC_{50} = 1.34 \pm 0.14 \mu M$) but less activity towards other cell lines, *i.e.*, colon, breast and melanoma, compared to the aliphatic cyclic amide

analogues 22 and 27. Comparing compounds 39 and 41, compound 39, containing 2-phenylpyridine, showed activity against colon cancer cells ($IC_{50} = 2.96 \pm 0.10 \mu M$), whereas compound 41 showed no activity in all four cancer cell lines compared to compounds 39 and 40. According to this data, the compounds which contain aliphatic cyclic amide analogues showed higher anticancer activity in all three cancer cell lines than those containing biphenyl amide analogues.

In conclusion, theophylline compounds containing 1,2,3-triazoles with different amide analogues have been designed, synthesized and evaluated; these contain systematic

variations, such as electron donating groups, *e.g.* a methyl group, on the α -carbon atom at position 7 of the theophylline ring, and substitutions such as cyclic rings and biphenyls. Structure activity relationships were also established for the compounds. Although the role of the methyl group is still not clear, substitution of cyclic rings and biphenyl rings seems to be important for their activities against cancer cell lines.

From a medicinal chemistry perspective, each functional group provides specific properties and behaviours that allow drug molecules to exert their desired pharmacodynamic and pharmacokinetic effects. Any given functional group may play a significant role in overall water/lipid solubility, electronic effects, steric effects and ability to interact with specific biological targets.

Molecular docking studies

In order to better understand their structure–activity relationships, molecular docking studies of compounds 22–41 with various therapeutic targets of cancer were observed; this demonstrated that human epidermal growth factor receptor 2 shows significant dock scores, binding energies and binding affinities with all the compounds. Meanwhile, the majority of the compounds show moderate scores with other targets, *i.e.*, EGFR, VEGFR2 and aromatase.

Regarding the docking results and the binding affinity and binding energy calculations against HER2, 22, 27 and 36 showed the highest dock scores. Compound 22 shows two H-bonds with amino acids in the active site of HER2; its dock score, binding energy and binding affinity are -15.42 , -25.43 and 10.29 , respectively. The docking results revealed that amino acids Thr862 and Asp863, located in the binding pocket of the protein, played important roles. The oxygen atom of the C=O group acts as an H-bond acceptor; its oxygen atom formed two H-bonds, one with the OH of Thr862 (bond length 2.49 Å), and another with the N of Asp863 (bond length 2.82 Å). Similarly, compound 27 showed two H-bonds, with a dock score, binding energy and binding affinity of -15.23 , -9.673 and 10.95 , respectively. The hydrogen atom of the amine group formed one H-bond with the oxygen atom of Asp863 by donating an electron pair; the bond length is 1.55 Å. The nitrogen atom of the theophylline ring formed one H-bond with the OH of Ser783 by accepting an electron pair; the bond length is 2.71 Å.

Compound 36 formed four H-bonds with active site amino acid residues, with a dock score, binding energy and binding affinity of -16.71 , -25.52 and 14.10 , respectively. The 6th position-OH of theophylline acts as an H-bond acceptor; also, its oxygen atom formed two H-bonds, one with the OH of Ser783 (bond length: 2.66 Å) and another with the OH of Thr798 (bond length: 2.76 Å). The oxygen atom of the C=O group formed one H-bond with the OH of Thr862 by accepting an electron pair; the bond length is 2.86 Å. In the biphenyl ring, the nitrogen atom formed one H-bond with the NE of Arg849 by accepting an electron pair; the bond length is 2.89 Å. Based on this characterization of protein–ligand interactions, it is evident that theophylline, 1,2,3-

triazole and amide analogues played key roles in forming H-bond interactions in both *in vitro* and *in silico* studies. The docking calculations of all the compounds (22–41) are also depicted in Table S5 in the ESI.†

Toxicity risk assessment screening

The amide analogues (22–41) were screened for their toxic properties, such as irritant, mutagenic, tumorigenic and reproductive effects, using Molinspiration and the Osiris server. The server contains a built-in list of about 5300 distinct substructure fragments created from 15 000 commercially available fragments with reported drug scores and drug likenesses. A drug score associated with drug likeness, $\text{clog}P$, molecular weight and toxicity risks may be used as a total value to judge the overall potential of a compound for use as a drug. The toxicity screening of all the compounds (22–41) showed no risk of mutagenic, tumorigenic, irritant or reproductive toxicity (Table S3 in the ESI.†).

Theoretical evolution of ADME properties

The bioavailability of amide analogues (22–41) was determined by ADME (Adsorption, Distribution, Metabolism and Excretion) using the MOE QSAR (Molecular Operating Environment Quantitative structure–activity relationship) model descriptor module. In order to explore the drug-like properties of compounds (22–41), the lipophilicity, expressed as the octanol/water partition coefficient and referred to here as $\log P(\text{o/w})$, as well as other theoretical calculations, such as molecular size, TPSA, number of hydrogen bond acceptors and donors, and number of rotatable bonds, were calculated for each compound (Table S4 in ESI.†).

Lipinski and colleagues defined the properties and molecular features that are associated with orally active drugs in humans and summarized then in the rule-of-five.³¹ Veber and co-workers later added additional related criteria.³² These parameters have been widely used as a filter for new potential drugs. Therefore, a computational study was performed to predict the physico-chemical parameters of the synthesized compounds to verify if the substances could full fill Lipinski's rule-of-five.

The physico-chemical properties of the studied amide analogues (22–41) were summarized (Table S4.†). Compounds (22–41) showed $\log P(\text{o/w})$ values below 5 which is favorable features for their oral bioavailability. TPSA represents the hydrogen bonding capacity of molecules with less than 140 Å are recognized to have good intestinal absorption. It is being expressed here as topological surface area (TPSA) which is sum of the surface areas occupied by oxygen and nitrogen atoms and the hydrogen's attached to them.

On the other hand hydrogen bonding capacity of drug candidate is also described by the number of hydrogen donors and acceptors. The compounds in this series showed H-donors >5 and H-acceptors >10 . The number of rotatable bonds is also important factor for the coefficient binding to receptors and channels as well as for the oral

bioavailability.³² Molecules with more than 10 rotatable bonds tend to show poor oral bioavailability. All studied compounds showed low conformational flexibility with less than 10 rotatable bonds.

The violation of more than one of these rules may indicate problems in the bioavailability of the potential drugs. The results showed that all compounds complied with Lipinski's rule (Table S4†), with exception slightly higher values were observed in TPSA, even in high molecular size more than 500. Finally summarizing the physico-chemical properties of the amide analogues (22–41), we could conclude that almost they obey the rule-of-five and meet all criteria for good solubility and permeability.

Conclusion

In the present work, an efficient, clean and convenient synthesis of novel theophylline analogues containing 1,2,3-triazoles with different amide groups has been designed. The procedure offers several advantages, including simple reaction conditions as well as simple experimental and product isolation procedures. Here, a series of twenty novel compounds were synthesized in good yield and characterized. This work focused on the anticancer activities of chemically diverse theophylline analogues containing 1,2,3-triazoles; the synthesized compounds 22, 27, 36 and 40 showed significant inhibitory activity against one or more tested cancer cell lines viz., lung (A549), colon (HT-29), breast (MCF-7) and melanoma (A375). Also, the docking results correlated with the IC₅₀ data and enabled analysis of the importance of specific interactions for describing the binding energies and binding affinities of different amide derivatives. The obtained results also showed that structural modification of theophylline can yield products with different pharmacological activities than those commonly associated with theophylline analogues, such as asthma, COPD and adenosine receptor antagonism. Therefore, this class of compounds could be a good starting point to develop new leads in the treatment of cancer. To demonstrate the utility of this chemistry, several biologically important molecules were synthesized; further studies are required to design more specific and efficient molecules.

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