RESEARCH ARTICLE

One Pot Synthesis of 1-(phenyl)-1H Indoles, their Biological Screening and ADME Studies

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ABSTRACT

This research aims to develop a novel way for synthesizing indole derivatives. 1-(phenyl)-1H-indole analogues were synthesized by cyclization of 1-phenyl-2-(phenyl amino)-ethane-1-one. Biological evaluation of title compounds and absorption, distribution, metabolism and excretion (ADME) studies were performed and title compounds had a higher affinity and created ample interactions with different proteins.

Keywords: ADME, Indole, Cyclization, Trifluoro acetic acid.

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INTRODUCTION

Indole is an important feature of many drugs.[1] The indole nucleus is found in a broad range of naturally occurring animal and vegetable products. Most products with an indole a basic moiety have a high level of physiological activity and some have incredibly complicated structures.[2] The utility of indole scaffolds in the synthesis of new therapeutic molecules has long been acknowledged.[3,4] Indoles are synthesized using a variety of intramolecular and intermolecular synthesis methods. The indole unit is a key factor in numerous biologically active compounds as alkaloids that have stimulated the new developmental area of organometallics.[5] The mechanism of nitrogen-containing heterocyclic molecules encircles anti-cancer drug-induced organ damage. The physiological features of the indole compound anticipated it to be a useful drug-like molecule, and its mode of action is predictable through the inhibition of reactive oxygen species (ROS) and inflammation.[6] Heterocyclic compounds with indole moiety are useful tools in our daily lives, with broad applications including sanitizers, pharmaceuticals and antioxidants.[7-11] The indole nucleus to a physiologically active pharmacophore also transformed it into a significant heterocyclic molecule with extensive biological activity.[12] Looking towards these important features of indole and distinct pharmacological actions, authors innovated the title indoles.[13,14] In addition to this research using the ADME web tool, physicochemical properties, pharmacokinetic profiles and drug-likeness were estimated.[15]

MATERIALS AND METHODS

General

The reaction was monitored using TLC silica gel. Melting points were uncorrected and measured using a capillary. Bruker Avance SX400 model used for recording IR spectra. PMR and ^{13}C spectra chronicled by Bruker (400 MHz) NMR instrument using $CDCl_3$ and $DMSOd_6$ solvents for dissolution of compounds. Chemical shift measurements were provided in parts per million (ppm). MS-MS was used to capture mass spectra (Direct Mass).

Synthesis

Experimental Scheme – Synthesis of 1-(phenyl)-1H Indoles

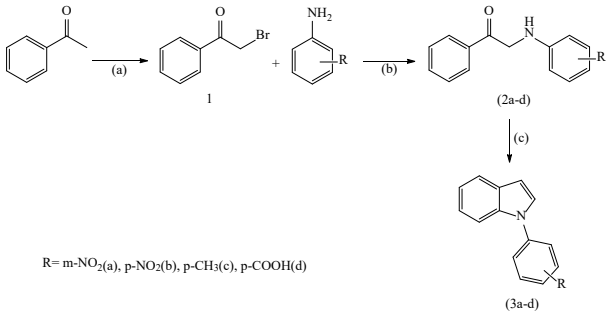

Figure 1: Reagent and condition of indole derivatives synthesis: (a) Br_2, glacial acetic acid, 0–5°C; (b) Ethanol, reflux, 6 hours; (c) TFA, acetic acid, reflux in the dark for 5–8 hours.

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Procedure

General synthesis of phenacyl bromide (1)

In 4.85 mL (0.04036 moles) Acetophenone has placed in a glass stoppered 250 mL conical flask and cooled to 5–10°C. In 2.5 mL (0.0443 moles) Br_2 liquid in 25 mL glacial acetic acid was added using an additional funnel with stirring in 20 minutes at 5–10°C. The reaction mixture kept on stirring to attend room temperature (25–35°C). The invisibleness of the yellow color marks reaction completion. In 100 gm of crushed ice was added to the reaction mixture (RM) to isolate the product. RM filtered after being separated mass through a Buckner funnel and dried. Hot water was used for crystallization, Yield: 96.88%, Color: Creamy white, M.P: 50°C, PMR ($CDCl_3$, 400MHz) δ 4.48 (S, 2H), 7.54 (t, 2H), 7.68 (t, 1H), 8.11 (d, 2H); MS (m/z): 197.90; C_8H_7BrO requires 197.97. Anal. Calc. for C, 48.27; H, 3.54; O, 8.04 Actual C 48.27; H 3.54; O 8.04.

General synthesis of 1-phenyl-2 (phenyl amino)-ethane-1-one analogues (2a-d)

Charged phenacyl bromide [1] (0.01 moles), different aniline analogs (0.021 moles) and 20 mL of absolute ethanol in a 100 mL-3N-RBF and raised temperature for reflux and maintained 6 hours. The reaction mixture was laid to cool to 25 to 35°C, filtered, washed using petroleum ether, and recrystallized in methanol.

- *2-((3-nitro phenyl) amino)-1-phenyl ethan-1-one (2a)*

Yield: 95.11%; M.P: 90°C; IR (in KBr) (cm^{-1}): 3349 (N-H), 2825 (C-H), 1688 (C=O), 1621 (N=O), 1267 (N=O), 1621–1530 (olefinic carbon), 1342 (C-N), 1222–1075 (C-H), 752 (Ar-Mono substituted); PMR ($CDCl_3$): d = 4.66 (s, 2H), 6.76–6.79 (m, 3H), 7.23–7.28 (m, 2H), 7.51–7.57 (m, 2H), 7.63–7.68 (m, 1H), 8.05 (d, 2H); ^{13}C NMR ($CDCl_3$): d = 196.95, 149.50, 148.38, 134.11, 133.49, 130.15, 128.80, 127.09, 118.62, 112.30, 52.69; MS (m/z): 257.3; $C_{14}H_{12}N_2O_3$ requires 256.08. Anal. Calc. for C, 65.62; H, 4.72; N, 10.93 Actual C, 65.50; H, 4.96; N,10.56.

- *2-((4-nitro phenyl) amino)-1-phenyl ethan-1-one (2b)*

Yield: 94.56%; M.P: 122°C; IR (in KBr) (cm^{-1}): 3359 (N-H str.), 2839 (C-H), 1681 (C=O), 1594 (N=O), 1270 (N=O), 1518-1444 (Olefinic carbon), 1370 (C-N), 1177–1027 (C-H), 754 (Ar-Mono substituted); PMR ($CDCl_3$): d = 4.65 (s, 2H), 6.71-6.90 (m, 3H), 7.55 (m, 2H), 7.70 (m, 1H), 8.00–8.15 (m, 4H); ^{13}C NMR ($CDCl_3$): d =195.48, 153.80, 136.36, 135.11, 133.21, 128.70, 128.62, 127.65, 114.60, 60.52; MS (m/z): 257.30 (M); $C_{14}H_{12}N_2O_3$ requires 256.08. Anal. Calc. for C, 65.62; H, 4.72; N, 10.93 Actual C, 65.26; H, 4.10; N, 10.92%.

- *1-phenyl-2-(p-tolyl amino) ethan-1-one (2c)*

Yield: 93.02%.; M.P. 119°C; IR (in KBr) (cm^{-1}): 3364 (N-H str.), 1659 (C=O), 1597, 1504 (C=C, Ar); PMR ($CDCl_3$): d = 2.28 (s, 3H), 4.63 (s, 2H), 6.27 (s, 1H), 6.67 (d, 2H), 7.06 (d, 2H), 7.45–7.56 (m, 2H), 7.62–7.67 (m, 1H), 8.05 (d, 2H); ^{13}C NMR (DMSO-d6): d = 195.80, 142.88, 133.72, 133.99, 129.66, 128.84, 127.71, 127.41, 115.58, 50.33, 20.22; MS (m/z): 226.42 (M); $C_{15}H_{15}NO$ requires 225.12. Anal. Calc. for C, 79.97; H, 6.71; N, 6.22. Actual C, 79.65; H, 6.53; N, 6.79%.

- *4-((2-oxo-2-Phenyl ethyl) amino) benzoic acid (2d)*

Yield: 91.55%; M.P: 130°C; IR (in KBr) (cm^{-1}): 3356 (N-H str.), 1702 (-COOH), 1318 (C-N str.), 1392 (-CH_2 str.), 2911 (C-H str.), 1018-1173 (CH Bend p-substituted), 853-837 (C-H Bend), 739-696 (Ar-R Bend substituted), 1670–1700 (C=O str.) cm^{-1}; PMR ($CDCl_3$): d = 4.52 (s, 2H), 6.18 (s, 1H), 6.95 (d, 2H), 7.57 (d, 2H), 7.68 (dd, 1H), 7.79 (d, 2H), 8.12 (dd, 2H), 12.04(s, 1H); ^{13}C-NMR (DMSO-d6): d = 195.23, 169.31, 151.72, 135.1, 133.1, 130.29, 128.9, 128.6, 118.61, 112.09, 60.52; MS (m/z): 256.20 (M); $C_{15}H_{13}NO_3$ requires 255.09. Anal. Calc.: C, 70.58; H, 5.13; N, 5.49 Actual C, 70.73; H, 5.43; N, 5.02%.

Synthesis of 1-(phenyl)-1H-indoles (3a-d)

Charged 1-phenyl-2 (phenylamino)-ethane-1-one analogs (0.0039 moles) (2a-d), trifluoroacetic acid (0.0082 moles), 10 mL glacial acetic acid in a 100 mL RBF. Reaction mixture refluxed for 5 hours. In 100 g of crushed ice was added to the RM. The separated mass was filtered followed by purification with petroleum ether: methanol.

- *1-(3-nitrophenyl)-1H-indole (3a)*

Yield: 75%; M.P: 126°C; IR (in KBr) (cm^{-1}): 3391 (N-H str.), 1680 (C=O), 1617 (olefinic carbon), 1529 (N=O), 1349 (N=O str.); PMR ($CDCl_3$): d = 6.45 (d, 1H), 6.75 (m; 1H), 7.30 (m, 1H), 7.58 (d, 1H), 7.73 (d, 1H), 7.80-7.93 (m, 4H) 8.01 (d, 1H), 8.11 (dd, 1H, -CH); ^{13}C-NMR (DMSO-d6): d = 142.72, 137.17, 133.71, 130.26, 129.86, 128.31, 127.51, 126.61, 122.7, 119.71, 107.1, 103.7, 100.1; MS (m/z): 237.7 (M); $C_{14}H_{10}N_2O_2$ requires 238.25. Anal. Calc.: C, 70.58; H, 4.23; N, 11.76 Actual C, 70.55; H, 4.58; N, 11.90%.

- *1-(4-nitrophenyl)-1H-indole (3b)*

Yield: 79.80%; M.P: 178°C, IR (in KBr) (cm^{-1}): 3055, 3027 (C-H str.), 1680 (olefinic carbon), 1598 (N=O Asymmetric Stretch), 1377 (N=O symmetric Stretch), 1315 (C-N str. Aromatic), 1206-1157 (C-H Bend p-disubstituted), 1103-1001 (C-H Bend o-disubstituted), 874, 763; PMR ($CDCl_3$): d = 5.61 (1H, s), 6.60(1H, d), 7.01 (2H, d), 7.15 (1H, d), 7.23 (2H, d), 8.00 (2H, d), 8.11(1H, s); ^{13}C NMR (DMSO-d6): d = 145.01, 144.06, 135.67, 130.12, 128.77, 125.93, 124.69, 120.02, 119.07, 109.50, 104.81; MS (m/z): 237.51 (M); $C_{14}H_{10}N_2O_2$ requires 238.25. Anal. Calc.: C, 70.58; H, 4.23; N, 11.76. Actual C, 70.65; H, 4.30; N, 11.40%.

1-(p-tolyl)-1H-indole (3c)

Yield: 80.85%; M.P: 140°C; IR (in KBr) (cm^{-1}): 3074 (C-H Str.), 1681, 1594, 1502 (olefinic carbon), 1496 (CH_3 Bend), 1321 (C-N St. Aromatic), 1177, 1108, 1029 (C-H bend p-disubstituted), 837 (C-H Bend); PMR ($CDCl_3$): d = 2.45 (s, 3H), 6.45 (d, 1H), 6.98 (m, 1H), 7.23 (d, 2H), 7.30-7.42 (m, 3H), 7.60 (d, 1H), 7.77 (d, 2H); ^{13}C NMR (DMSO-d6): d = 137.69, 136.42, 135.71, 130.10, 129.41, 128.31, 127.41, 121.41, 120.11, 118.42, 109.41, 103.60, 26.11 MS (m/z): 207.4 (M); $C_{15}H_{13}N$ requires 207.10. Anal. Calc.: C, 86.92; H, 6.32; N, 6.76 Actual C, 86.50; H, 6.56; N, 6.94%.

- *4-(1H-indol-1-yl) benzoic acid (3d)*

Yield: 65.10%; M.P: 170°C; IR (in KBr) (cm^{-1}): 3351 (N-H str.), 3057 (-CH str.), 2630 (-OH in COOH), 1677 (C=O str.), 1601

(olefinic carbon), 1174-1103 (C-H Bend p-substituted), 825 (C-H Bend), 767 (C-H Bend O-substituted); PMR ($CDCl_3$): d = 6.99 (d, 1H), 7.87 (d, 2H), 8.08 (d, 2H), 8.30 (d, 3H), 8.37 (d, 2H), 11.33 (s, 1H, Broad COOH); ^{13}C NMR (DMSO-d6): d = 169.01, 142.88, 134.69, 130.12, 129.81, 129.45, 128.01, 127.81, 126.69, 121.71, 121.71, 120.69, 108.45, 102.12; MS (m/z): 238.18 (M); $C_{15}H_{15}NO$ requires 237.08. Anal. Calc.: C, 75.94; H, 4.67; N, 5.90 Actual C, 75.84; H, 4.85; N, 5.77%.

RESULTS AND DISCUSSION

The title compound amino indoles are synthesized by cyclization of 1-phenyl-2 (phenylamino)-ethane-1-one analogs in trifluoro acetic acid. Phenyl acyl bromide reacted with aromatic substituted amines in ethanol to generate 1-phenyl-2 (pphenylamino-ethane-1-one analogs 2a-d which on cyclization with trifluoro acetic acid yields title indoles 3a-d. All synthesized entities were evaluated and verified by using ^1H-NMR, ^{13}C-NMR, FTIR, and MS-MS. These entities were subjected to biological evaluation.

Antibacterial Activity

The synthesized moieties screened for the effectiveness to microorganisms *Enterobacter* (gm-ve), *E. coli* (gm-ve), *Staphylococcus aureus* (gm+ve) and *Bacillus subtilis* (gm+ve) at 100 ppm (10 mg/mL) dilution in DMSO (dimethyl sulfoxide). Standardization was done using ampicillin. Innovated entities exhibit magnificent potency against *Enterobacter*, *S. aureus and B. subtilis* microorganisms.

Cultures

The cultures (*Enterobacter, E. coli, S. aureus and B. subtilis*) were spread in nutrient agar (10 mm) containing a petri plate for 24 hours using the Kirby-Bauer method.[16] Each synthesized substance was applied to the plates in an aseptic manner after being diluted with dimethyl sulfoxide (DMSO) (0.2 mL of 10 mg/mL). To measure the antimicrobial activity, the vicinity of bacterial growth inhibition produced by diffusion of chemicals from the well into the surrounding media was measured using a standard scale as the plates had been incubated for 1 day at

Table 1: Zone of inhibition by 1-phenyl-2 (phenyl amino)-ethane-1- one analogues (2a-d) & 1-(phenyl)-1H-indoles (3a-d)

Compound no./Reference drug	*Conc. (µg/mL)*	*Microorganisms and zone of inhibition*			
		Gm-Ve bacteria		*Gm+Ve bacteria*	
		Enterobacter	*E. coli*	*Staphylococcus aureus*	*Bacillus subtilis*
2a	10	12	-	10	10
2b	10	20	-	11	11
2c	10	16	-	11	11
2d	10	20	-	18	18
3a	10	12	14	21	30
3b	10	12	13	17	21
3c	10	12	11	9	15
3d	10	18	29	20	16
Ampicillin (Reference drug)	10	10	10	9	10

Table 2: Swiss ADME results of indole derivatives in comparison with standard Ibuprofen and BHT

Compound id	*2a*	*2b*	*2c*	*2d*	*3a*	*3b*	*3c*	*3d*	*BHT*	*Ibuprofen*
Rotatory bonds	5	5	4	5	2	2	1	2	2	4
H-bond acceptors	3	3	1	3	2	2	-	2	1	2
H-bond donors	1	1	1	2	-	-	-	1	1	1
MR	74.29	74.29	70.45	72.42	72.1	72.1	68.24	70.23	71.97	62.18
TPSA	74.92	74.92	29.1	66.4	50.75	50.75	4.93	42.23	20.23	37.3
MLOGP	1.44	1.44	2.86	1.02	2.89	2.89	3.52	2.78	4.12	3.13
Consensus Log P	2.18	2.16	3.09	2.09	2.79	2.92	3.73	2.77	4.37	3
ESOL Solubility (mg/mL)	7.21 E-02	7.21 E-02	3.46 E-02	1.14 E-01	2.38 E-02	8.37 E-03	8.78 E-03	3.71 E-02	6.00 E-03	9.09 E-02
GI absorption	High	High	High	High	High	High	High	High	High	High
BBB permeant	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Pgp substrate	-	-	-	-	-	-	-	-	-	-
Lipinski violations	-	-	-	-	-	-	2	-	-	-
Muegge violations	-	-	-	-	-	-	1	-	2	-
PAINS alerts	-	-	-	-	-	-	-	-	-	-
Leadlikeness violations	-	-	2	-	1	2	2	1	2	1

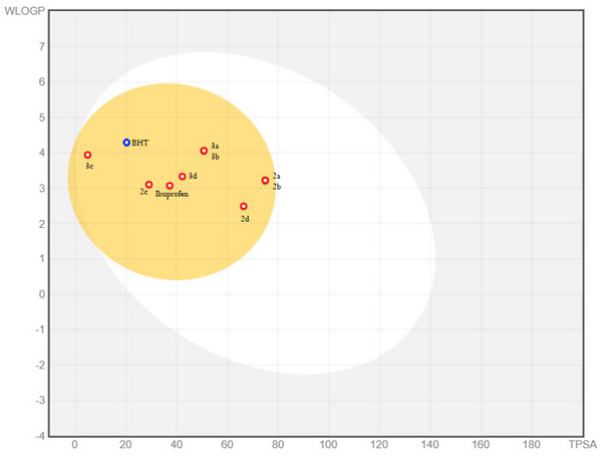

Figure 2: Boiled-Egg model of indole analogues and standard BHT and Ibuprofen.

35°C to evaluate the antimicrobial activity. Ampicillin is used as a referral drug.

ADME Studies

SWISS-ADME web tool used, offered by the Swiss Institute, the pharmacokinetic characteristics and oral bioavailability profile of the novel compound's indole derivatives were anticipated and are shown in Table 2 and Figure 1.

Overall, it was projected that all of the examined indole and their analogs would have adequate physical, chemical, and pharmacokinetic features, with zero violations of Lipinski's regulation of five and no pains. According to above regulation, every compound predicted logPo/w in the range of 1.02 to 3.52 is expected for a system with 1 to 5 rotational bonds, 0 to 3 hydrogens are having bond acceptors properties, 0 to 2 hydrogens are having bond donors' properties, a molar refractivity (MR) is around 62.18 to 74.29, a topological polar surface area between 20.23 and 74.92. Along with that, they have higher GI absorption and moderate water solubility. These results provide significant evidence for the possible oral bioavailability of these substances.[17,18]

CONCLUSION

Targeted indole analogs are synthesized by cyclization of 1-phenyl-2 (phenylamino)-ethane-1-one analogs which were synthesized with condensation of phenacyl bromide with different aromatic amines and well characterized. Amino indoles showed excellent antimicrobial potency with *Enterobacter, E. coli, S. aureus* and *Bacillus* strains. The insertion of NO_2 group at mata position and COOH group at para position enhances antimicrobial activity. ADME studies are designed to investigate how a living organism processes a chemical or drug. absorption distribution metabolism and excretion (ADME) studies of the compounds show that there is no side effect on the central nervous system (CNS). ADME profiles are moderately water soluble, mostly blood-brain-barrier (BBB) with non-permeant. These compounds offer an encouraging foundation for future lead optimization and medication development.

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REFERENCES

1. Kaushik NK, Kaushik N, Attri P, Kumar N, Kim C, Verma A, Choi E. Biomedical Importance of Indoles. Molecules. 2013;18:6620-6662. Available from: doi.org/10.3390/molecules18066620
2. Kogl, F, Haagen-Smit AS, Erxleben HZ. Physiol. Chem. 1934; 228(90): 104-113. Available from: doi.org/10.1038/267019a0
3. Somei M, Yamada F. Simple indole alkaloids and those with a non-rearranged monoterpenoid unit. Natural Product Report. 2005;22:73. Available from: doi.org/10.1039/B316241A
4. Chang FJ, Rangisetty JB, Dukat M, Setola V, Raffay T, Roth B, Glennon RA. 1,2,3,4-Tetrahydrocarbazoles as 5-HT6 serotonin receptor ligands. Bioorg. Med. Chem. Lett. 2004;14:1961. Available from: 10.1016/j.bmcl.2004.01.071
5. Gao D, Li A, Guan L, Zhang X, Wang L Y. Solvent-dependent ratiometric fluorescent merocyanine dyes: Spectral properties, interaction with BSA as well as biological applications. Dyes Pigments, 2016;129:163. Available from: doi.org/10.1016/j.dyepig.2016.02.020
6. Li JJ, Gribble GW. Palladium In Heterocyclic Chemistry: A Guide for The Synthetic Chemistry. Elsevier Science Ltd, Oxford, Uk. 2000
7. Robinson B, The Fischer Indole Synthesis, John Wiley and Sons, New York. 1982. Available From: doi.org/10.1007/3-540-30031-7_104
8. Jia C, Lu W, Kitamura T, Fujiwara Y. Highly Efficient PdCatalyzed Coupling of Arenes with Olefins in the Presence of tertButyl Hydroperoxide as Oxidant. Org Lett. 1999;1:2097–2100. Available from: doi.org/10.32657/10356/45490
9. Sniady A, Morreale MS, Wheeler KA, Dembinski R. Room Temperature Electrophilic 5-endo-dig Chlorocyclization of Alk-3-yn-1- ones with the Use of Pool Sanitizer: Synthesis of 3-Chlorofurans and 5-Chlorofuropyrimidine Nucleosides. Eur.J. Org. Chem. 2008;3449-3452. Available from: doi.org/10.1002/ejoc.200800397
10. Cocuzza A J, Chidester D R, Cuip S, Fitzgerald L, And Gilligan P. Use of the Suzuki reaction for the synthesis of arylsubstituted hetrocycles as corticotropin-releasing hormone(crh) antagonists. Bioorg. Med. Chem. Lett. 1999;9:1063-1066. Available from: doi.org/10.1016/s0960-894x(99)00133-x
11. Vitaku E, Smith DT, Njardarson JT. Analysis of the Structural Diversity, Substitution; Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem. 2014;57:10257-10274. Availble from: doi.org/10.1021/jm501100b
12. Vitaglione P, Fogliano V. Use of antioxidants to minimize the human health risk associated to mutagenic/carcinogenic heterocyclic amines in food. J. Chromatogr. B. 2004;802:189-199. Available from: doi.org/10.1016/j.jchromb.2003.09.029
13. Abdel-Wahab BF, Awad GE, Badria FA. Synthesis, antimicrobial, antioxidant, anti-hemolytic and cytotoxic evaluation of new imidazole-based heterocycles. Eur J Med Chem. 2011;46:1505–1511. Available From: doi.org/10.1016/j.ejmech.2011.01.062
14. Sharma V, Pardeep K, Devender P. Biological Importance of The Indole Nucleus in Recent Years A Comprehensive Review. J Heterocycle Chem. 2010; 47: 491-502. Available from: doi.org/10.1002/jhet.349

15. Daina A, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Nature: Scientific Reports. 2017;7(1)42717. Available from: doi.org/10.1038/srep42717
16. Bauer AW, Kirby WMM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Path, 1996;45(4):493-496. Available from: doi.org/10.1093/ajcp/45.4_ts.493
17. Muegge I, Heald SL, Brittelli D.Simple selection criteria for drug-like chemical matter. Journal of Medicinal Chemistry. 2001;44(12):1841-6. Available from: doi.org/10.1021/jm015507e
18. Teague S, Davis A, Leeson P, Oprea T. The design of leadlike combinatorial libraries. Angewandte Chemie International Edition England. 1999;38:3743–3748. Available from: doi.org/10.1002/(SICI)1521-3773(19991216)38:24<3743::AID-ANIE3743>3.0.CO;2-U