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AN EXPEDIENT DOMINO CLICK APPROACH TO THE SYNTHESIS OF FACE 'A' 1,2,3-TRIAZOLO ANNULATED ANALOGUES OF 1,4-BENZODIAZEPINES OF MEDICINAL INTEREST

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ABSTRACT: The present work describes a concomitant formation of the 1,2,3 –triazole and 1,4-benzodiazepine rings in one step through a domino process by bringing an alkyne appended fragment in close proximity to the azide function to allow it to undergo a 1,3 dipolar cycloaddition reaction , to produce face 'a' 1,2,3-triazolo annulated 1,4-diazepines . This concept of synthesis has been applied to 2-[2'-imino methylene ethyne]-3-azido substituted derivative of 1,4-benzodiazepines and indole, to deliver the face 'a' 1,2,3- triazolo annulated analogues of 1,4-diazepino condensed benzodiazepines[3] and indoles. The 3-azide derivatives was in turn prepared by the diazotization of corresponding amine with [bmim]NO_2 ionic liquid, in presence of HCl, followed by its treatment with [bmim]N_3 ionic liquid, [bmim] = 1-benzyl-3-methyl imidazolium chloride. The noteworthy feature of this reaction was that it facilitated the formation of products in environmentally benign solvent free aqueous medium. The compounds were evaluated the anti-oxidant and anti-microbial activities.
KEYWORDS:1,4-Diazepines, oxoketenedithioacetals, 1,2,3-triazoles, antibacterial activity, antifungal activity, antioxidant activity.

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I. Introduction

1,4-Diazepines and 1,2,3-triazoles exhibit remarkable pharmacological properties[1]. The ubiquitous presence of 1,4-diazepines and 1,2,3-triazoles derivatives in the chemical literature and the wide array of impressive biological activities which they show has, stimulated intense research efforts to be directed towards the synthesis of their structural analogues where in different constitution and biological activities in the new material could allow them to be used as novel chemotherapeutic agents[2-5].

II. Experimental

Melting points were determined in open capillaries and are uncorrected. Purity of the compounds was checked by TLC in Silica gel G plates. PMR spectra were recorded on Bruker Avances 400 II spectrometer using TMS as internal reference. Chemical shifts are expressed in terms of δ ppm through out. IR spectra were recorded on Bruker (KBr) spectrophotometer. Wave number is expressed in cm^{-1}. Physical data and spectral data of the compounds are given in Table-1 and Table-2.

Synthesis of (2-cyano-phenyl)-(2-oxo-2-phenyl-ethyl)-carbamic acid ethyl ester (3)[6-11]

2-Aminobenzonitrile (1) (0.22g.,0.02mol) was mixed with sodium carbonate (0.44g., 0.02mol)and to this was dropwise added ethyl chloro formate (2.0ml,0.02 mol) in ethanol (5ml) and the mixture was strirred continously for 4 hrs at low temperature in ice bath. The solid which settled was filtered,washed with cold water , recrystallized from rectified spirit and water to give (2-cyano-phenyl)-carbamic aid ethyl ester (2) . A solution of compound (2) (0.4g.,0.02 mole) in DMF(4.0 ml) and ethanol (10.0ml) was stirred in an ice cold bath . Sodium hydride ((0.7gm, 0.01 mol) was added with stirring . After 15 min. of continuous stirring phenacyl chloride (1.46g.,0.02mol) was added portionwise and the mixture was strirred overnight at room temperature. The solid which settled was filtered, washed with cold water , extracted with ethyl acetate. The organic layer was washed with brine solution and concentrated to yield a yellow solid which on further evaporation and cooling gave yellow crystals of (2-cyano-phenyl)-(2-oxo-2-phenyl-ethyl)-carbamic acid ethyl ester (3) which were collected and recrystallized in methyl cyanide to give 3 yield 0.94g.

Synthesis of 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester (7), 3-azido-2-benzoyl-4-methyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester (8) and 1,2,3-triazolo-5-phenyl-[1,4]-diazepino[6,7-c]-N-ethoxycarbonyl-N-4-methyl[1,4]-benzodiazepine-2-one (9)

To a solution of (2-cyano-phenyl)-(2-oxo-2-phenyl-ethyl)-carbamic acid ethyl ester (3) (0.64g , 0.02 mol) in dry ethanol (2.0 ml) , carbon disulfide (0.64 ml,0.04mol) was added to a cool suspension of potassium tertiary butoxide (1.6g.,0.04mol) in dry benzene and DMF (10:6 ml) at 0°C. The reaction mixture was allowed to stand at room temperature for 4 hrs. Methyl Iodide (2.82ml,0.02mol) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 hrs at room temperature with occasional shaking and then refluxed on a water bath for 4-6 hrs. . After the completion of reaction, the aqueous portion was extracted with benzene and the combined extract were washed, neutralized with 5% aqueous HCl, filtered and dried. The product (1-benzoyl-2,2-bis methylsulfanyl-vinyl)-(2-cyano-phenyl)-carbamic acid ethyl ester (4) thus obtained was purified by crystallization in ethyl acetate to give brown coloured solid mass which was purified by silica column. A solution of compound 4 (0.02mol) was mixed to methyl amine (2ml) and was added to a cool suspension of potassium tertiary butoxide in DMF with continous stirring for 1 hr to give (1-benzoyl-2-methylamino-2-methylsulfanyl-vinyl)-(2-cyano-phenyl)-carbamic acid ethyl ester (5) which was refluxed for 3-4 hrs. to give 2-benzoyl-5-imino-4-methyl-3-methylsulfanyl-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester (6). The mixture was poured into ice water, neutralised and was dried over rotatory evaporator. The desired solid product 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester (7) obtained was recrystallised with ethylacetate, yield 1.08gm.

To a solution of 7 (0.63g.,0.02mol) in tertiary butanol and water (1:1mix, 5ml), copper sulfate (0.66g.,0.02mol) and sodium ascorbate (2.8g.,0.02mol) were added. After 15 min. sodium azide (1.4g., 0.02mol) was added to this mixture and the reaction mixture was stirred for 8h to give 8. The mixture was diluted with water and a solution of 3-azido-2-benzoyl-4-methyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester (8) in ethyl acetate was added with propargyl amine (0.87g., 0.02mol) and the mixture was stirred for 4-5 hrs and poured into ice water and extracted with ethylacetate and dried over anhydrous sodium sulfate and evaporated under reduced pressure, which was precipitated using n-hexane to give 1,2,3-triazolo-5-phenyl-[1,4]-diazepino[6,7-c]-N-ethoxycarbonyl-N-4-methyl[1,4]-benzodiazepine-2-one (9) as a thick brown colored viscous mass, which was dried over rotatory evaporator to give yield 0.96g.

Synthesis of 3-amino-2-benzoyl-indole-1-carboxylic acid ethyl ester (11), 3-azido-2-benzoyl-indole-1-carboxylic acid ethyl ester (12) and 1,2,3-triazolo-5-phenyl-[1,4]diazepine--indole-1-carboxylic acid ethyl ester (13)[12-17] :

A solution of **3** (0.64g,0.02mol) was taken in DMF (2.5ml) and stirred for 15 min., sodium hydroxide (2.2g)was added to it portion wise with continuous stirring and the solution was stirred at room temperature for 3 hrs to give **11.** To this a mixture of $NaNO_2$ solution in H_2O + HCl (1.30g:1.37ml) (1:1) was added with continuous stirring at room temperature for 1 hr. To this a solution of NaN_3 (1.4g., 0.02mol) was added and kept it for further stirring for two hrs at room temperature to give **12**.

In an alternate method ionic liquid [bmim]Cl (0.15gm, 0.002mol) was stirred with a solution of $NaNO_2$ (1.46g,0.02mol) for half an hr and a solution of NaN_3(1.4g., 0.02mol) was added with continuous stirring for 1 hr. To this, a solution of **11**(0.86g,0.02mol) in water was added and the mixture was stirred for 3hrs to give **12** as a brown colored solid.

To a solution of **12** in tertiary butanol and water (1:1mix, 5ml) was added copper sulfate ($CuSO_4.5H_2O$) (0.66g.,0.02mol)) and sodium ascorbate (2.8g., 0.024mol). the mixture stirred for 15 min., then propargyl amine (0.87g.,0.02mol) was added and stirred for 4h**.** It was diluted with water and extracted with ethylacetate, the organic layer was dried and evaporated to afford pure 1,2,3-triazolo-5-phenyl-[1,4]diazepine--indole-1-carboxylic acid ethyl ester **(13)** as a light brown coloured viscous mass which was recrystallised with ethyl acetate to give yield 1.23g.

Synthesis of 10-methyl-9-oxo-3-phenyl-9,10-dihydro-1H-1,2,4,10-tetraaza-benz[*f*] azulene-4- carboxylic acid ethyl ester (14) and 10-methyl-9-oxo-3-phenyl-9,10-dihydro-1-oxa-2,4,10-triaza-benzo[*f*] azulene-4-carboxylic acid ethyl ester (15):

Hydrazine hydrate (1.0ml, 0.04mol) was added to the sodium methoxide (1.12g, 0.06mol) in absolute methanol (15ml) and stirred for 10 min seperately. To each of these mixture, 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **(7)** (1.54g,0.02mol) was added after which the solvent was evaporated under reduced pressure. The reaction mixture was cooled and the solid separated was filtered and washed with di ethyl ether. The pure compound (14) was obtained by recrystalised with ethanol, and purified by silica column yield 0.76g.

Hydroxylamine hydrochloride (1.78g, 0.04mol) was added to sodium methoxide (2.12g, 0.04mol) in absolute methanol (15ml) and stirred for 10 min., to this 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (1.54g, 0.04mol) was added and the mixture was evaporated under reduced pressure. The mixture was then poured on crushed ice. The solid mass was separated

by filteration and washed with diethyl ether. The pure compound (15) was obtained by recrystallized and purified by silica column from ethanol. yield 0.98gm, yield.

Synthesis of 11-methyl-2,10-dioxo-4-phenyl-1,2,10,11-tetrahydro-1,3,5,11-tetraaza dibenzo[*a,d*]cycloheptene-5-carboxylic acid ethyl ester (16a), 11-methyl-10-oxo-4-phenyl-1,2-thioxo-1,2,10,11-tetrahydro-1,3,5,11-tetraaza-dibenzo[*a,d*]cycloheptene-5-carboxylic acid ethyl ester (16b), 2-amino-11-methyl-10-oxo-4-phenyl-1,2,10,11-tetrahydro-1,3,5,11-tetraaza-dibenzo[*a,d*]cycloheptene-5-carboxylic acid ethyl ester (16c) and 11-methyl-2-methylene-10-oxo-4-phenyl-1,2,10,11-tetrahydro-1,3,5,11-tetraaza dibenzo[*a,d*]cycloheptene-5-carboxylic acid ethyl ester (16d):

To a mixture of urea (1.52,0.02mol), sodium ethoxide(0.14g, 0.002mol) and ethanol (20-25ml) was added 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (1.27g,0.02mol) and refluxed for 8h. The solvent was removed by distillation and the residue was treated with glacial acetic acid(3-5ml)) just enough to dissolve sodium salt of the pyrimidine and refluxed for 15min. The obtained solid product was then filtered, evaporated, recrystallized with ethanol and purified by silica column to give compound 16 a, yield 0.97g.

To a mixture of thiourea (1.52g, 0.02mol), sodium ethoxide (0.14g, 0.002mol) and ethanol (20-25ml) was added 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester 7 (1.27g, 0.02mol) in refluxed for10hrs. The solvent was removed by distillation and the residue was treated with glacial acetic acid (3-5ml) just enough to dissolve sodium salt of the pyrimidine and refluxed for 15 min. The obtained solid product was then filtered, evaporated, recrystallized with ethanol and purified by silica column to give compound 16 b, yield 0.84g.

To a solution of 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester 7 (1.27g, 0.02mol) in ethanol (25ml) was added guanidine nitrate (30.0g, 0.167mol) and sodium acetate (27.0g, 0.334mol). The mixture was heated under reflux for 40 h. The obtained solid product was then filtered, evaporated, recrystallized with ethanol and purified by silica column to give compound 16 c, yield 0.76g.

To a solution of compound 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (1.27g.,0.02mol) in ethanol (25ml) was added acetamidine hydrochloride (1.54g, 0.167mol) and sodium acetate (27.0g, 0.334mol). The mixture was heated under reflux for 48 h. The obtained solid product was then filtered, evaporated, recrystallized with ethanol and purified by silica column to give compound 16 d, yield 0.84g.

Synthesis of 6-methyl-7-oxo-13-phenyl-1,6,7dihydro-5*H*-5,6,12,14-tetraaza-dibenzo[*b,h*]heptalene-12-carboxylic acid ethyl ester (17a), 6-methyl-7-oxo-13-phenyl-1,6,7dihydro-5-thia-,6,12,14-triaza-dibenzo[*b,h*]heptalene-12-carboxylic acid ethyl ester (17b) and 6-methyl-7-oxo-13-phenyl-1,6,7dihydro-5-oxa-,6,12,14-triaza-dibenzo[*b,h*]heptalene-12-carboxylic acid ethyl ester (17c):

A mixture of o-phenylene diamine (1.08g,0.01mol), 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (0.625g,0.01mol) and ethanol (25-30ml) was refluxed for 4h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. The obtained solid product was extracted with chloroform, washed with water, dried over sodium sulphate and purified by silica column to give **17a**, yield 0.83g.

A mixture of o-aminothiophenol (1.25g,0.01mol), 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (0.625g,0.01mol) and ethanol (25-30ml) was refluxed for 3h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. The obtained solid product was extracted with chloroform, washed with water, dried over sodium sulphate and purified by silica column to give **17b**, yield 0.81g.

A mixture of o-aminophenol (1.09g,0.01mol), 2-benzoyl-4-methyl-3-methylsulfanyl-5-oxo-4,5-dihydro-benzo[e][1,4]diazepine-1-carboxylic acid ethyl ester **7** (1.27g,0.02mol) and ethanol (25-30ml) was refluxed for 5h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. The obtained solid product was extracted with chloroform, washed with water, dried over sodium sulphate and purified by silica column to give 17c, yield 0.85g.

III. Result And Discussion

The present endeavour provided an efficient synthetic entry of triazole ring to the 1,4-benzodiazepine nucleus through the application of a novel multicomponent one pot process from 2-amino benzonitrile (1).

The conversion of 1 to 1,2,3-triazolo 1,4-benzodiazepine derivatives 9 and 13 (scheme-1(a), (b) took place through two protocols. The first method proceeded through the formation oxoketene dithioacetal 4 from (2-cyanophenyl)-(2-oxo-2-phenyl ethyl)-carbamic acid ethyl ester (3) from its reaction with and carbon disulphide and CH_3I in the presence of base t-BuOK. The subsequent reactions propelled forward from this

through three main steps to deliver finally the target molecule 9 through a one pot domino click approach in its last steps which was effected in the presence of a Cu catalyst through the reaction of propargyl amine on 8.

The key step in the second reaction involved the formation of an indole derivatives 11 from 3, through the reaction of later with a base. The subsequent strategy involved the most recorded method of preparation of face 'a' triazolo annulated analogues of 1,4-benzodiazepines that proceeded through a domino approach between propargyl amine and o-azido benzophenone derivatives. This strategy was applied the on 2-benzoyl-3-azido substituted derivative of indole 12 to furnish 13 from its reaction with propargyl amine that acted an active partner to initiate the domino reaction with 12 to give 13. The IR, 1HMR, C13 and mass spectra of 9 and 13 substantiated the structures assigned. The IR spectrum showed absorption bands at 1800 and 1630 cm-1 due to C=O and C=N, 1285 and 1506 cm^{-1}due to N-N=N and N=N a broad band at 3170 cm^{-1}due to NH. The 1HMR spectrum of 9 and 13 exhibited a singlet at 7.4 and 7.56 of NH- of triazole, another singlet at 4.81 and 4.12, integrating for two protons of $–CH_2$- group and a multiplet at 7.29-7.62 and 7.18-7.93 for aromatic protons. Their mass spectrum showed molecular ion peaks at 429 *m/z* and 372 *m/z* , respectively corresponding to the molecular weight and the fragmentation pattern of compound 9 and 13 also confirmed the structure assigned to these. The C13 spectrum of 9 and 13 exhibited peaks at 143 and 131 for the carbon of of 1,2,3-triazole, 164 for the carbon of imine and other aliphatic and aromatic carrbons.

An inspection of the structure of the intermediate 7(scheme 2) motivated us to utilize their potential to these annulations of these molecules with five, six and seven membered rings, such as with pyrazole, isoxazole, pyrimidine and 1,4-benzodiazepine (thiazepine and oxazepine). Treatment of 7 with bidentate nucleophiles such as hydrazine hydrate, hydroxylamine hydrochloride , with urea, thiourea, guanidine, acetamidine and with o-phenylene diamine, o-aminothiophenol, o-aminophenol gave 14, 15, 16 (a-d) and 17(a-c) respectively (scheme 2).

Table 1 The physical data of compounds

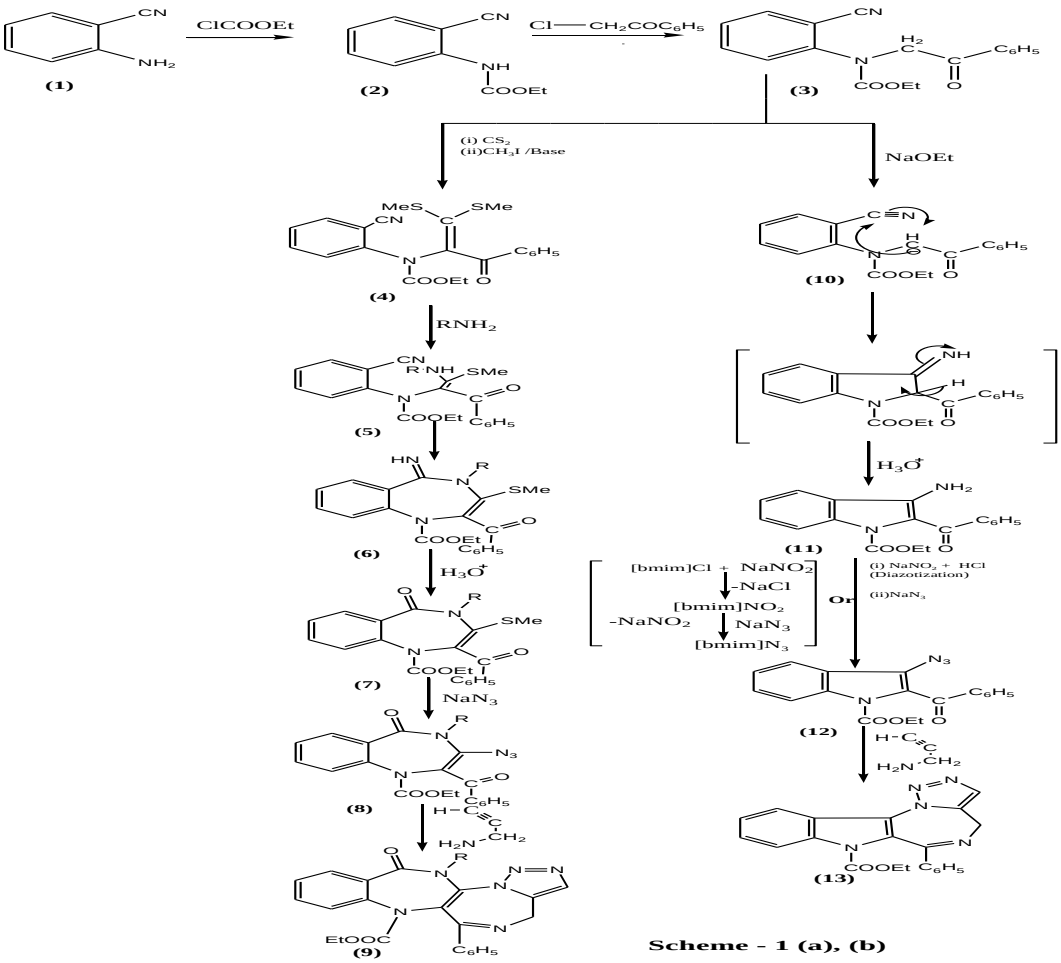
S. No. I	Compound II	Mol.wt. III	Mol.formula IV	M.P.(°C) V	Yield (%) VI	C Calcd./ Found	H Calcd. /Found	N Calcd./ Found	S Calcd. /Found
1	3	308.33	$C_{18}H_{16}N_2O_3$	158-160	89	70.12/ 70.61	5.23/ 5.46	9.09/ 9.36	_
2	4	412.53	$C_{21}H_{20}N_2O_3S_2$	178-180	85	61.14/ 61.41	4.89/ 4.58	6.79/ 6.82	15.55/ 15.82
3	7	396.46	$C_{21}H_{20}N_2O_4S$	209-210	81	63.62/ 63.34	5.08/ 3.34	7.07/ 7.39	16.14/ 16.34
4	9	428.44	$C_{23}H_{20}N_6O_3$	180-182	80	64.48/ 64.75	4.71/ 4.84	19.62/ 19.45	_
5	13	371.39	$C_{21}H_{17}N_5O_2$	208-210	74	67.91/ 67.70	4.61/ 4.52	18.86/18.49	_
6	14	362.38	$C_{20}H_{18}N_4O_3$	230-232	79	66.29/ 66.60	5.01/ 5.28	15.46/ 15.32	_
7	15	363.37	$C_{20}H_{17}N_3O_4$	234-235	80	66.11/ 66.49	4.72/ 4.63	11.56/ 11.37	_
8	16a	390.39	$C_{21}H_{18}N_4O_4$	265-267	79	64.61/ 64.28	4.65/ 4.49	14.35/ 14.21	_
9	16b	406.46	$C_{21}H_{18}N_4O_3S$	268-270	74	62.05/ 62.44	4.46/ 4.36	13.78/ 13.69	7.89/ 7.72
10	16c	389.41	$C_{21}H_{19}N_5O_3$	270-272	70	64.77/ 64.53	4.92/ 4.70	17.98/ 17.80	_
11	16d	390.44	$C_{22}H_{22}N_4O_3$	268-270	74	67.68/ 67.33	5.68/ 5.56	14.35/ 14.42	_
12	17a	438.48	$C_{26}H_{22}N_4O_3$	279-280	73	71.22/ 71.46	5.06/ 5.26	12.78/ 12.69	_
13	17b	455.53	$C_{26}H_{21}N_3O_3S$	281-282	71	68.55/ 68.74	4.65/ 4.36	9.22/ 9.30	7.04/ 7.24
14	17c	439.46	$C_{26}H_{21}N_3O_4$	278-279	70	71.06/ 71.24	4.82/ 4.74	9.56/ 9.35	_

Table 2: Interpretation of spectral data with the help of IR (cm^{-1}) (KBr), ^{13}C-NMR, ^{1}H-NMR and Mass (MS (m/z)) of compound 2.003 -2.018

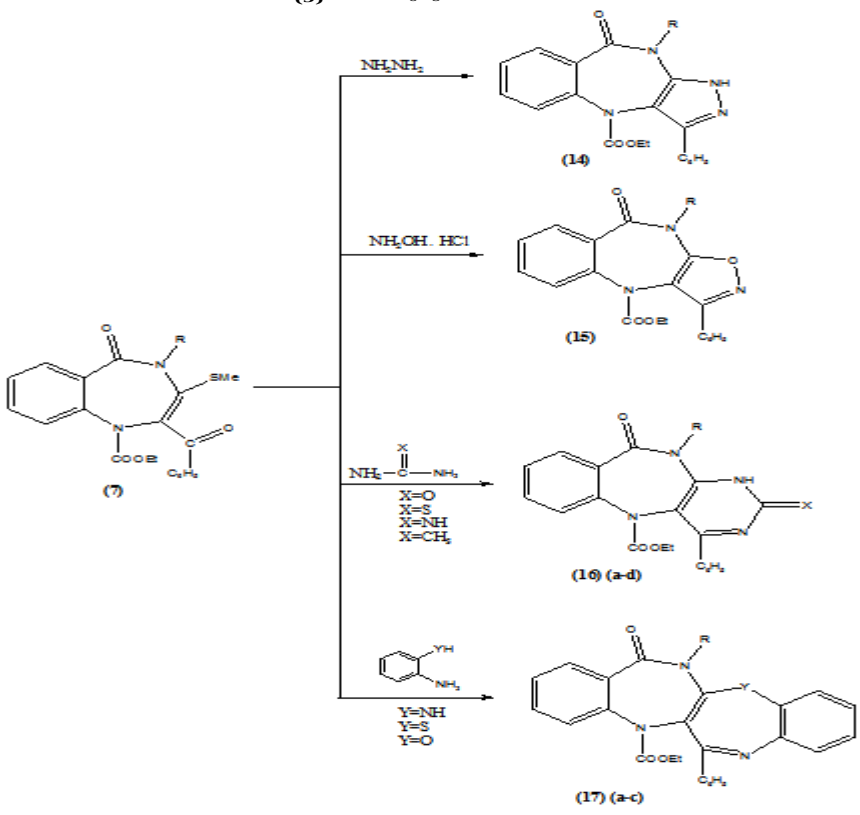
S.No I	Compound II	^{1}H NMR (DMSO) δ(ppm) and MS; m/z (relative abundance) III	^{13}C NMR ($CDCl_3$)δ (ppm) IV
1	3	7.18,7.52,7.82,7.49(4H,m,Ar-C(1-benzene)) 4.22,4.12(2H,s,CH_2, methylene) 7.37-7.86(5H,m,Ar-H) 1.30(3H,s,CH_3) **MS,m/z:302.2(M^+70%), 305.0(28.6%), 309.12(20.4%),310.12(2.7%), 308.12(100.0%).**	Ar-C[124.8(CH),133.0(CH), 121.1 (CH) , 141.70(C), 104.4(C), 132.20(CH)] Ar-C[137.4 (C), 128.6(CH), 128.4 (CH), 132.9(CH),128.4(CH), 128.6(CH) ,acetoacetate] 165.0(C of amide) 116.5(C of nitrile- C_6) 196.5(C of carbonyl(-CO), -C_6) Al-C[59.7(CH_2)(sterric correction), 13.3 (C), 57.2 (C)]
2	4	2.25 (3H,s,CH_3) 4.12(2H,s,CH_2) 7.18-7.82(4H,m,Ar-H,NC(=O)(1-benzene)) 7.45-7.81(5H,m,Ar-H,-C=O) 1.30(3H,s,CH_3,-CO(=O)) 2.25(3H,s,CH_3, α-S-C=C)) **MS,m/z:396.3(M^+80%)),318.1(19.5%), 413.09(25.7%),414.09(9.4%), 412.09(100.0%)**	Ar-C[124.8(CH),133.0(CH),121.1 (CH),141.7 (C), 104.4(C), 132.2(CH)] Ar-C[136.7(C),129.7(CH),129.0 (CH),134.3(CH), 129(CH), 129.7(CH)] [115.7 (C), 138.3(C), ethylene] 116.5(C of 1-nitrile) 149.4(C of N-amide) Al-C[13.2(CH_3),13.3(CH_3),57.3(CH_2), 13.2(CH_3)] 187(C of (–CO) carbonyl)
3	7	7.18-7.93(4H,m,Ar-H(1-benzene)) 7.45-7.81(5H,m,Ar-H) 2.74,(3H,m, CH_3) 4.12(3H,s, CH_2) 2.25(3H,s, CH_3) 1.30(3H,s,CH_2) **MS,m/z:378.3(M^+30%), 396.11(100.0%), 397.12(23.8%),398.11(4.6%),141.0(23%)**	Ar-C [124.2(CH) ,132.1(CH), 120.5 (CH), 137.0(C), 125.4(C), 127.5(CH)] Ar-C[136.7(C),129.7(CH),129.5 (CH),134.3(CH), 129(CH), 129.7(CH)] 107.4,127.3 (C of CH_2 ethylene) 149.5(C of amide) 187.0 (C of carbonyl) 162.8(C of N-amide) Al-C[29.8(CH_3), 13.3(CH_3), 57.3 (CH_2), 11.7(CH_3)]
4	9	1.30(1H,s,CH_3 –OC(=O)) 2.74(3H,s,CH_3) 7.18-7.93(4H,m,Ar-H(1-benzene)) 7.29-7.62(5H,m,Ar-H) 7.4(IH,s,NH of triazole ring) 4.81(2H,s,CH_2) 4.12(2H,s,CH_2, -OC(=O)N) **MS,m/z:410.3(M^+27.0%),351.4(29.9%),429.16(27.6%),430.17(3.2%),428.16(100.0%),144.2(40.0%)**	Ar-C[124.2(CH), 132.1(CH), 120.5 (CH), 137.0(C), 125.4(C), 127.5(CH)] Ar-H [137.3(C), 129(C), 128.6(CH), 130.8(C), 128.6(C), 129.0(C)] 162.8, 149.4(C of amide) 164.6 (C of N-imine) 92, 108 (CH_2 of ethylene) Al-C[28.4(CH_3), 37(CH_2), 13.3 (CH_3),57.3(CH_2)] 143(triazole C of 1-pyrrole) 131(triazole C)
5	13	7.0-7.6(4H,m,CH of 1-indole) 7.29-7.62(5H,m,CH of bezylidenimin, Ar-H)	Ar-C-[122(CH), 120(CH), 111(CH), 136(C) , 128(C), 121(CH)] Indole-[102(C), 124(C) pyrrole]

		7.56(H,s,1,2,3-triazole) 4.81, 4.20(2H,s,CH_2) 1.30(3H,s,CH_3) **MS,m/z:396.3(M^+70.0%),371.14(100.0%),372.14(25.5%),373.14(3.4),315.1(52%),152.2(39.8%)**	Ar-C[137.3(C) ,129(CH), 128.6 (CH), 130.8(CH), 128.6(CH), 129.0(CH)] 164.6(C of 1-imine) Al-C [42.5(CH_2), 13.3(C), 57.3 (CH_2)] 161(C of carboxyl) 143, 131(C of 1,2,3-triazole)
6	14	7.18-7.93(4H,m,Ar-H(1-benzene)) 13.7(1H,s,NH of 3-pyrazole) 7.32-7.48(5H,m,Ar-H) 2.74, 1.30(3H,s,CH_3) 4.12(2H,s,CH_2) **MS,m/z:312.3(M^+70.0%),362.14(100.0%),363.14(22.6%),364.14(3.3%),315.1(52%),152.2(39.8%)**	Ar-C[124.2(CH),132.1(CH),120.5 (CH), 137.0 (C), 125.4(C), 127.5(CH)] Ar-C [136.5(C), 127.0(CH), 129.0 (CH) ,128.5 (CH), 129.0(CH),127.0(CH)] 150.3,163.7(C of amide) 138.2, 144.2,115.8(C of pyrazole, -N) Al-C [13.3(CH_3). 57.2(CH_2), 35.2(CH_3), carbonyl]
7	15	7.18-7.93(4H,m,Ar-H(1-benzene)) 2.74, 1.30(3H,s,CH_3) 7.48-7.32(5H,s,Ar-H) 4.12(2H,s,CH_2) **MS,m/z:323.3(M^+70.0%),363.12(100.0%),364.13(22.7%),365.13(3.2%),315.1(52%),152.2(39.8%)**	Ar-C[124.2(CH),132.1(CH),120.05 (CH), 137 (C), 125.4 (C) , 127.5(CH)] Ar-C [136.5(C), 127.0(CH), 129.0(CH) ,128.5 (C), 129.0(CH), 127(CH)] 163.7, 150.3(C of amide) Al-C [35.2(CH_3), 13.3(CH_3), 57.2 (CH_2), carbonyl] 115.8,144.2, 138.2 (3-isoxazoleC,)
8	16 a	8.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene)) 7.30-7.60(5H,m,Ar-H, bezylidenimin) 2.74, 1.30(3H,s,CH_3) 4.12(2H,s,CH_2 of methylene) **MS,m/z:383.3(M^+70.0%),390.13(100.0%),391.14(23.8%),392.14(3.5%),315.1(52%),152.2(39.8%)**	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C),127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] 149.40, 160 (C of amide) 164.6(C of imine) Al-C [28(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 88,109(C of ethylene CH_2) 162.80 (C of amide)
9	16 b	2.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene)) 7.30-7.60(5H,m,Ar-H, bezylidenimin) 2.74, 1.30(3H,s,CH_3) 4.12(2H,s,CH_2 of methylene) **MS,m/z:412.3(M^+70.0%),406.11(100.0%),407.11(25.8%),408.11(5.6%),315.1(52%),152.2(39.8%)**	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] 149.40 (C of amide) 182 (C of thioamide) 164.6(C of imine) Al-C [28(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 86,122 (C of ethylene CH_2) 162.80 (C of amide)
10	16 c	2.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene))) 7.30-7.60(5H,m,Ar-H, bezylidenimin) 2.74, 1.30(3H,s,CH_3) 4.12(2H,s,CH_2 of methylene) **MS,m/z:377.3(M^+70.0%),389.15(100.0%),390.15(25.6%),391.16(2.7%),315.1(52%),152.2(39.8%)**	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] 149.40 (C of amide) 163 (C of 1-imine) 164.6(C of imine) Al-C [28(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 86, 122 (C of ethylene CH_2) 162.80 (C of amide)
11	16 d	2.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene))	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)]

		7.30-7.60(5H,m,Ar-H, bezylidenimin) 2.74, 1.30(3H,s,CH_3) 4.12(2H,s,CH_2 of methylene) 1.32 (3H,s,H of CH_3 –N) 4.44(H,s,H of methine) **MS,m/z:396.3(M^+70.0%),390.17(100.0%),391.17(26.1%),392.18(3.0%),315.1(52%),152.2(39.8%)**	Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] 149.40 (C of amide) 163 (C of 1-imine) 164.6(C of imine) 148.4, 84 (C of ethylene CH_2) Al-C [28.4(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 84, 112 (C of ethylene CH_2) 162.80 (C of amide)
12	17 a	4.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene)) 6.50-7.0(4H,m,Ar-H) 7.29-7.63(5H,m,Ar-H, bezylidenimin) 2.74, 1.30 (3H,s,CH_3) 4.12(2H,s,CH_2 of methylene)) **MS,m/z:412.3(M^+70.0%),438.17(100.0%),439.17(30.5%),440.18(4.2),315.1(52%),152.2(39.8%)**	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] Ar-C [139.8 (C), 140.2(C), 122.8 (CH) ,119.80 (CH), 127.8(CH), 116.4(CH)] 149.40 (C of amide) 163 (C of 1-imine) 164.60(C of imine) Al-C [28.4(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 84, 118 (C of ethylene CH_2) 162.80 (C of 1-amide)
13	17 b	4.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene)) 7.0-7.20(4H,m,Ar-H) 7.29-7.62(4H,m,Ar-H, bezylidenimin) 2.74 ,1.30(3H,s,CH_3 (carbonyl)) 4.12(2H,s,CH_2 of	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] Ar-C [153.9(C), 126(C), 122.3 (CH) ,126.60 (CH), 127.3(CH), 130.5(CH)] 149.40 (C of amide) 163 (C of 1-imine) 164.6(C of imine) Al-C [29.8(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 96, 117 (C of ethylene CH_2) 162.80 (C of amide)
14	17 c	4.0(1H,s,NH) 7.18-7.93(4H,m,Ar-H(1-benzene)) 6.70-7.10(4H,s, Ar-H) 7.29-7.62(5H,m,Ar-H, bezylidenimin) 2.74 ,1.30(3H,s,CH_3) 4.12(2H,s,CH_2 of methylene) 4.3,4.7 (H of ethylene) **MS,m/z:412.3(M^+70.0%),439.15(100.0%),440.16(29.4%),441.16(5.4%),315.1(52%),152.2(39.8%)**	Ar-C[124.20(CH),132.10(CH),120.50 (CH), 137 (C), 125.4(C), 127.5(CH)] Ar-C [131.2(C), 129(CH), 128.6 (CH) ,130.80 (CH), 128.6(CH), 129(CH)] Ar-C [141.70(C), 150.20(C), 122.7 (CH) ,124 (CH), 127.7(CH), 118.3(CH)] 149.40 (C of amide) 163 (C of 1-imine) 164.6(C of imine) Al-C [27.2(CH_3), 13.3(CH_3), 57.3(CH_2), carbonyl] 86, 127 (C of ethylene CH_2) 162.80 (C of amide)



Scheme - 1 (a), (b)

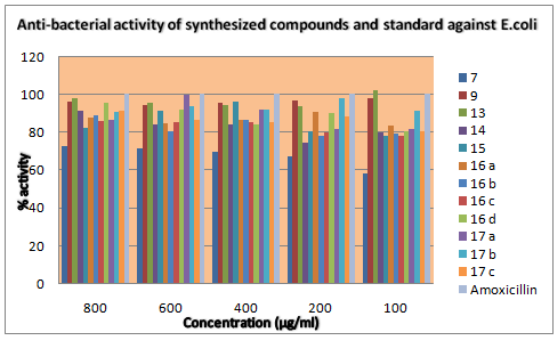


Scheme - 2

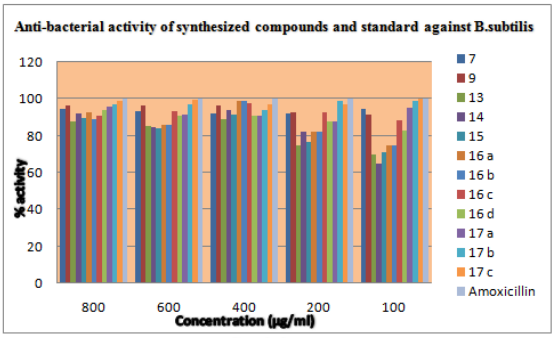
Antimicrobial activity

Compounds 7, 9, 13, 14, 15, 16(a-d) and 17(a-c) were evaluated for antibacterial activity against *Escherichia coli* (MTCC-119), *Bacillus subtilis* (MTCC-7419), *Staphylococcus aureus* (MTCC-9886) and *Pseudomonas aeruginosa* (MTCC-2453) and antifungal activity against *Candida albicans* (MTCC-183), *Aspergillus niger* (MTCC-8652), *Candida parapsilosis* (MTCC-1965) and *Candida tropicalis* (MTCC-9038) by using amoxicillin and fluconazol as standards for comparison for antibacterial and antifungal activity respectively. Cup-plate method and broth dilution method were used for the evaluation of antibacterial activity[18-20] and cup-plate and mycelial weight method were used for the evaluation of antifungal activity[21-23]. The results clearly indicated that increase in the concentration of compounds, increased the antibacterial activity. A regular fall in the activity was recorded when the concentration of the compounds were reduced. Results are expressed in the graphical form in graph 1-4 for antibacterial activity and graph 5-8 for antifungal activity by cup-plate method and graph 9and 10 respectively by broth-dilution and mycelial weight method.

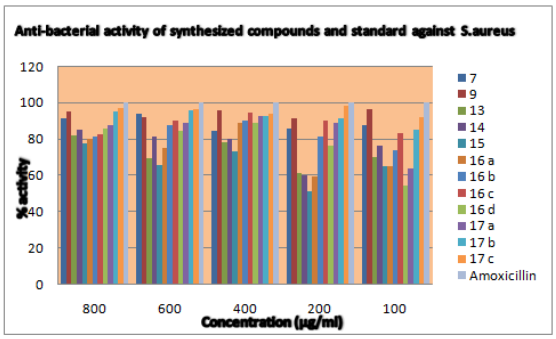
(i) Result of anti-bacterial activity by cup plate method



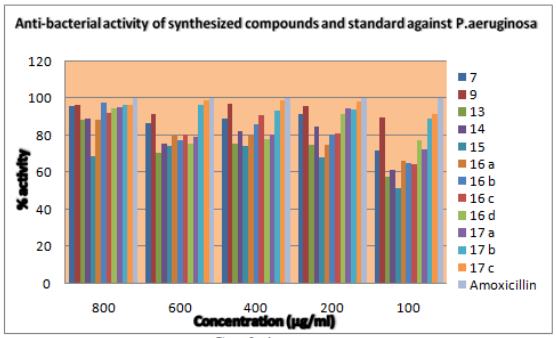
Graph 1



Graph 2

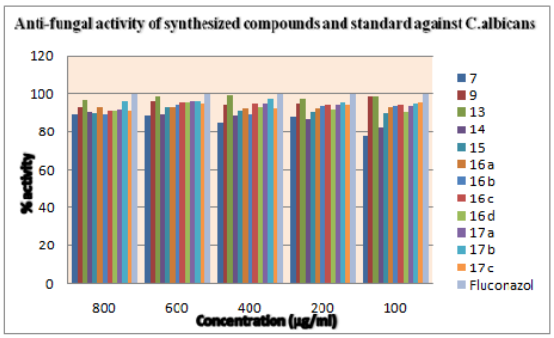


Graph 3

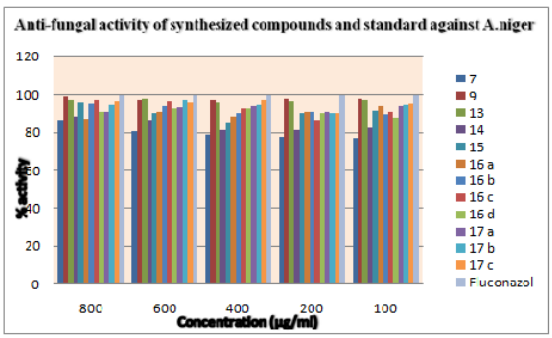


Graph 4

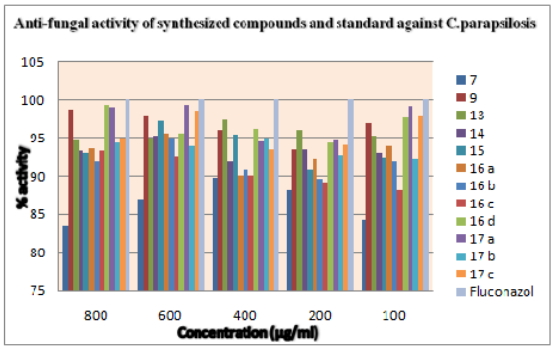
(ii) Result of anti-fungal activity by cup plate method



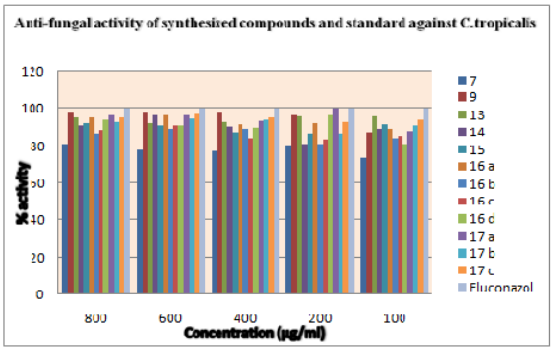
Graph 5



Graph 6

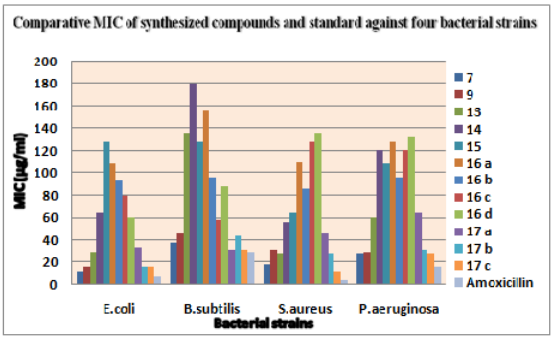


Graph 7

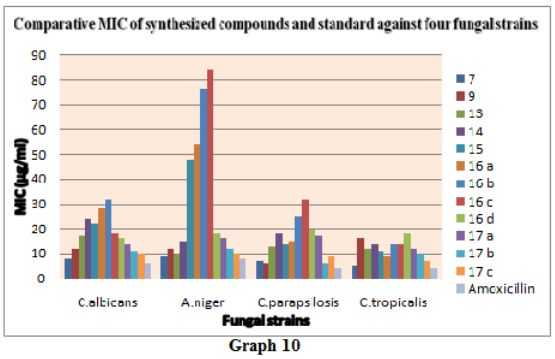


Graph 8

(iii) Result of anti bacterial by broth dilution method and anti fungal activity by mycelia weight method



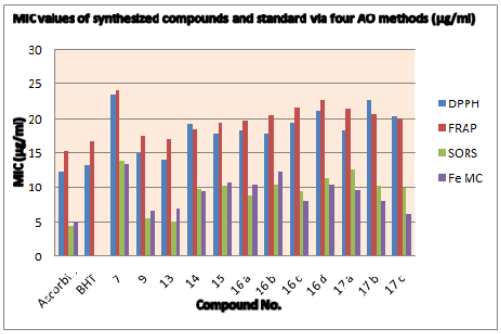
Graph 9



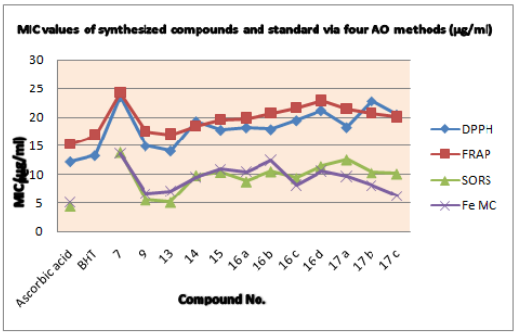
Graph 10

Antioxidant activity

The compounds were screened for antioxidant activity[24-28] by the four evaluating methods i.e by DPPH radical scavenging method, by Ferric ion reducing antioxidant power (FRAP) assay, by superoxide radical scavenging method and by Fe^{+2} ion chelating activity method to examine the radical scavenging capacity of synthesized compounds. Results indicated remarkable scavenging activity of the compounds in comparison with ascorbic acid. The higher antioxidant activity is reflected in a lower IC50 of the compounds. With an increase in concentration of the synthesized compound the ability of the antioxidants to quench the free radicals increased and decrease in absorbance was observed. The result have been presented in graphical form in graph **11** and **12.**



Graph 11



Graph 12

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