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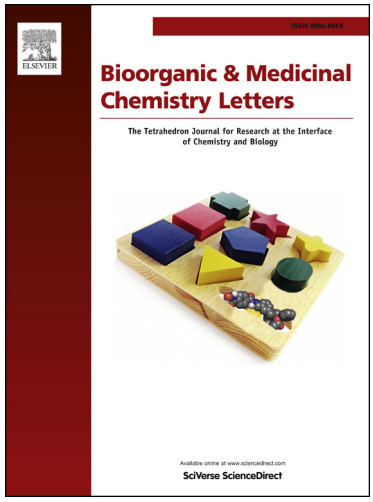

Studies on substituted benzo[h]quinazolines, benzo[g]indazoles, pyrazoles, 2,6-diarylpyridines as anti-tubercular agents

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Bioorganic & Medicinal Chemistry Letters - (2013) ---

Studies on substituted benzo[*h*]quinazolines, benzo[*g*]indazoles, pyrazoles, 2,6-diarylpyridines as anti-tubercular agents

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ABSTRACT

Various substituted 5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine, 1-(3-(4-alkoxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2*H* benzo[*g*]indazol-2-yl)ethanone, pyrazole and 2,6-diarylpyridine derivatives have been synthesized in good yields by an efficient methodology. The synthesized compounds (**4-23**) were evaluated for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain. Compounds **6a**, **6c**, **8a, 19a** and **19e** exhibited significant anti-tubercular activity at MIC values 50, 100, 50, 25 and 100 µM concentration. *In vitro* cytotoxicity data using THP-1 cells indicated that most active compound **19a** is safe as its MIC value is much lower than the cytotoxic value.

In coincidence with the spread of HIV infection,[1] tuberculosis is today amongst the universal health threats. Approximately 13 million new cases of tuberculosis each year worldwide; about one fifth of them are in India.[2] In 2011, there were an estimated 8.7 million new cases of TB and 1.4 million people died from TB. TB is one of the top killers of women, with 5,00,000 deaths among HIV women in 2011. India, China, the Russian Federation and South Africa have almost 60% of the world's cases of MDR-TB.[3] It is estimated that nearly 5,00,000 people die from the disease - more than 1000 per day.[5] As resistant strains of *Mycobacterium tuberculosis* (MTB) have slowly emerged, treatment failure is a main reality.[4] However, various drugs such as streptomycin (**i**), rifampicin (**ii**), pyrazinamide (**iii**), isoniazid (**iv**), ethionamide (**v**) and ethambutol (**vi**) etc (Figure 1) are used for the treatment of TB. Since, these are taking six month long time treatment,[6] therefore it becomes imperative for the discovery of some new chemical entity.

In the recent past, several benzo[*h*]quinazoline derivatives have been reported to exhibit antiplatelet combined with anti-inflammatory activity,[7] antimicrobial activity,[8] as well as protein kinase inhibitors,[9] antivirals,[10] antiproliferative,[11] histamine H_4 receptor (H_4R) antagonists,[12] human methionine aminopeptidase inhibitor-1,[13] thymidylate synthase inhibitors,[14] neoplasm inhibitors.[15] Some pyrimidine derivative (**vii**, Figure 1) and pyrazole analog (**ix**) are reported to be highly effective against *Mycobacterium tuberculosis* in *in vitro* model at 0.78 and 0.35 µg/mL concentration respectively.[16] 4-(2-(Piperidin-1-yl)ethoxy)styryl chain containing chalcone has shown *in vitro* 3.5 µg/mL activity against *Mycobacterium tuberculosis* with more than two fold high lipophilicity as comparison with Rifampicin (**ii**, Figure 1).[17] These findings[7-17] inspired us to synthesize 2-(*sec*.amines)ethoxy chain containing benzo[*h*]quinazolines (**6**) and analogs (**8,9,11**) in anticipation to display anti-tubercular activity with better efficacy.

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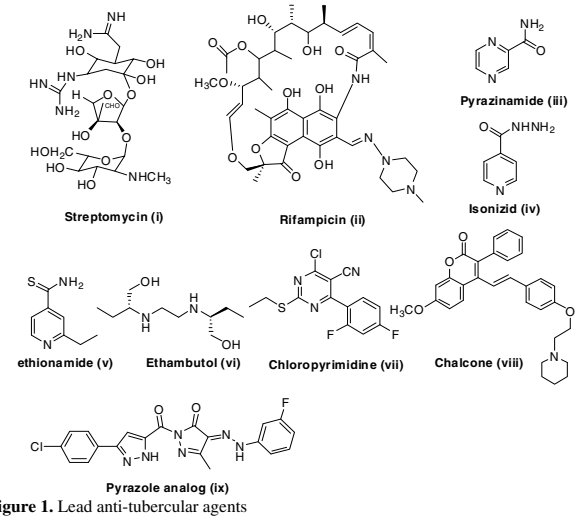
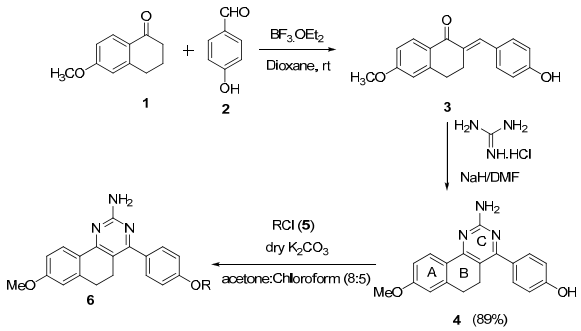
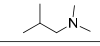


Figure 1. Lead anti-tubercular agents

In our synthetic strategy, 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**1**) and 4-hydroxybenzaldehyde (**2**) were selected as starting

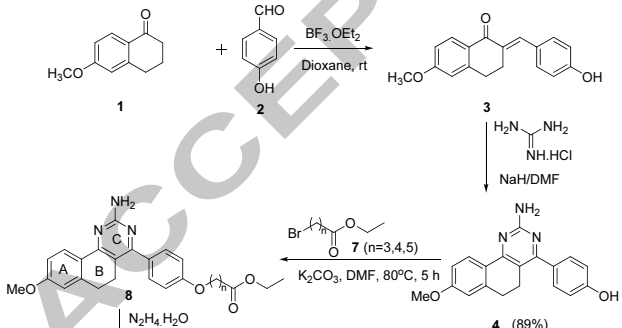
materials. Reaction of **1** with 4-hydroxybenzaldehyde (**2**) using $BF_3.OEt_2$ in dioxane at room temperature with stirring for 72 h produced precursor 2-(4-hydroxybenzylidene)-6-methoxy-3,4-dihydronaphthalen -1(2*H*)-one (**3**) which on further reaction with guanidine hydrochloride in the presence of sodium hydride and DMF gave 4-(2-amino-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-4-yl)phenol (**4**) in 89% yield, Scheme 1. Further, alkylation of 4-(2-amino-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-4-yl)phenol (**4**) with *sec*.amine substituted ethyl chloride (**5**) in presence of anhydrous potassium carbonate in dry acetone/chloroform gave 4-(4-(2-(*sec*.amine)ethoxy)phenyl)-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine (**6**) in 75-96% yields.



5/6	R	Mp	Yield of 6
a		154	89
b		120	96
c		115	84
d		105	75

Scheme 1. Synthesis of 4-(substituted)-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine (**6**)[21]

In anticipation to study structure activity relationship (SAR) of methoxybenzo[*h*]quinazolin-2-amine (**6**), we have also synthesized ethyl (4-(2-amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazolin-4-yl)phenoxy)alkanoate (**8**) and (4-(2-amino-8-methoxy-5,6-dihydrobenzo[*h*] quinazolin-4-yl)phenoxy)alkanehydrazide (**9**) in excellent yields (Scheme 2).

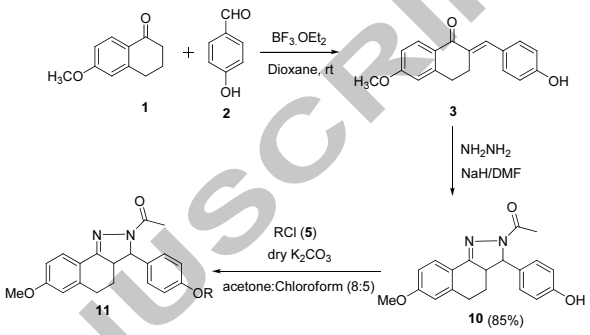


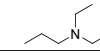
8/9	n	Mp (°C)	Yields (%)
8a	3	148-149	90
8b	4	109-110	94
8c	5	147-148	93
9a	3	228-229	92
9b	4	221-222	96
9c	5	164-165	91

Scheme 2. Synthesis of ethyl (4-(2-amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazolin-4-yl)phenoxy)alkanoate (**8**) and (4-(2-amino-8-methoxy-5,6-dihydrobenzo[*h*]quinazolin-4-yl)phenoxy)alkanehydrazide (**9**)[21]

Synthesis of compound **8** was performed though alkylation reaction of **4** using long chain esters (**7**, n = 3,4,5) in presence of anhydrous K_2CO_3 in dry DMF or acetone which yielded **8** in 90-94% yields. For synthesis of compound **9**, compounds **8** (1.0 eq) was subjected to amidation reaction using hydrazine hydrate (1.5 eq, 95%) in ethanol at reflux temperature which yielded compound **9** in 91-96% yields.

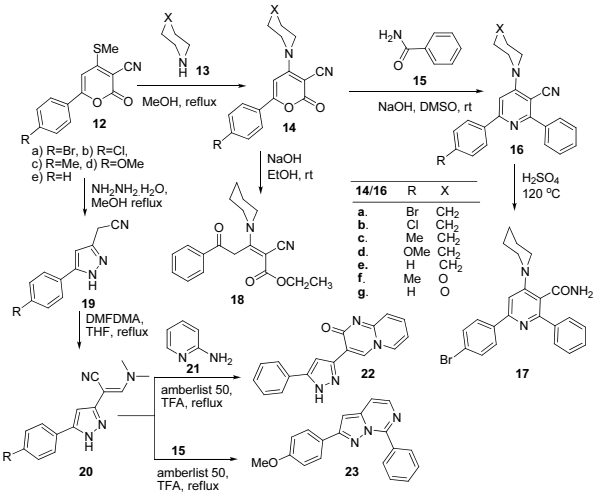
In our strategy to see the effect of size of ring C on biological efficacy of compound **6**, we further synthesized 1-(3-(4-hydroxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)ethanone (**10**) from the reaction of 2-(4-hydroxybenzylidene)-6-methoxy-3,4-dihydro- naphthalen-1(2*H*)-one (**3**) with hydrazine hydrate in the presence of sodium hydride and DMF, Scheme 3. Further, reaction of 1-(3-(4-hydroxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-2-yl)ethanone (**10**) with various *sec*-amine substituted ethyl chlorides (**5**) gave final product **11** in 72-80% Yields, Scheme 3.



10/11	R	Yield of 11
a		70
b		75
c		70
d		75
e		80

Scheme 3. Synthesis 1-(3-(4-alkoxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2*H*- benzo[*g*] indazol-2-yl)ethanone (**11**)[21]

Furthermore, the potential anti-tubercular activity of pyridine[6] and pyrazole[18] derivatives viz. isonized (**iv**) and ethionamide (**v**) (Figure 1), prompted us to explore anti-tubercular activity of 2,6-diarylpyridines (**16** and **17**), 2-cyano-5-oxo-5-phenyl-3-piperidin-1-yl-pent-2-enoic acid ethyl ester (**18**),[19] and pyrazole derivatives (**19-23**).[20]



14/16	R	X
a.	Br	CH_2
b.	Cl	CH_2
c.	Me	CH_2
d.	OMe	CH_2
e.	H	CH_2
f.	Me	O
g.	H	O

Scheme 4. Method of synthesis of **12,14,16-18** refer to reference [19] and method of synthesis of **19,20,22,23** refer to reference [20].

Synthesis of compound **16** and **17** was done starting from **12** through amination followed by base catalyzed condensation reaction

with **5** using reported methodology. Whereas compound **20** and **22** was synthesized via transformation of **12** into **19** using hydrazine hydrate in methanol at reflux. Compound **19** was converted into **20** using DMF-DMA in THF at reflux which yielded **20** in 76-85% yield. Compound **20** on condensation with 2-aminopyridine (**21**) and benzamide (**15**) in TFA at reflux temperature gave **22** and **23** in 31% and 36% yields respectively[19,20] Scheme 4.

Synthesized compounds **4-23** were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain using micro plate alamar blue assay (MABA) and results are reported in Table 1. Lipophilicity of the synthesized derivatives (**4-23**) were calculated using ChemBioDraw Ultra 11.0 and is expressed in the terms their log P value, Table 1.

Table 1.
In vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain using micro plate alamar blue assay (MABA) and *in vitro* cytotoxicity in THP-1 cells (CC_{50})

Compounds	MIC (µM)	Log P[a]	CC_{50}
4	>200	3.96	-
6a	50	4.96	200
6b	200	4.54	-
6c	100	4.23	200
6d	200	4.55	-
8a	50	4.67	200
8b	200	5.08	-
8c	200	5.50	-
9a	200	2.82	-
9b	200	3.28	-
9c	200	3.74	-
10	>200	2.88	-
11a	>200	3.88	-
11b	200	3.46	-
11c	200	3.15	-
11d	200	3.47	-
11e	200	3.82	-
16a	>200	6.77	-
16b	>200	6.50	-
16c	>200	6.43	-
16d	>200	5.82	-
16e	>200	5.95	-
16f	>200	5.03	-
17	>200	5.65	-
18	>200	1.82	-
19a	25	3.10	>200
19b	>200	2.82	-
19c	>200	2.75	-
19d	200	2.14	-
19e	100	2.27	>200
20a	>200	3.19	-
20b	>200	2.92	-
20c	>200	2.85	-
20d	100	2.23	>200
20e	200	2.36	-
22	>200	2.74	-
23	>200	3.94	-
Isonizid	0.2	-0.60	-
Rifampicin	2.0	2.61[17]	-
Streptomycin	6.0	-4.11[17]	-
vii (Figure 1)[16a]	0.78 [b]	4.74	
ix (Figure 1)[16b]	0.35 [b]	3.40	

[a]liphophilicity was calculated using ChemBioDraw Ultra 11.0, [b] **µg/mL**

The anti-tubercular activity results of synthesized compounds (**4-23**) revealed that starting precursor benzo[*h*]quinazoline (**4**) was inactive at 200 µM concentration (MIC value), while its 4-(4-(2-(piperidin-1-yl)ethoxy) chain containing analog (**6a**) and 4-(4-(2-(dimethylamino)ethoxy) chain containing analog (**6c**) exhibited significant anti-tubercular activity at MIC 50 µM and 100 µM respectively. Two other analogs (**6b** and **6d**) also found active at MIC value 200 µM. The long chain ester analog of **4** (**8a**) exhibited activity at MIC value 50 µM, while alkanoate derivatives (**8b** and **8c**) and alkanylhydrazide derivatives (**9a-c**) showed activity at 200 µM. Structure activity relationship (SAR) reveled that piperidine substituted analog (**6a**) and propanoate chain containing analog (**8a**) had better activity as compared with other related analogs. It is notworthy that alkanylhydrazide (**9a-c**) had only moderate activity, although these derivatives contain –$CONHNH_2$ group similar to the clinically useful drug isonizied (**iv**, Figure 1).

As similar to benzo[*h*]quinazoline (**4**), the five membered ring containing precursor benzo[*g*]indazole (**10**) was found inactive at 200 µM, whereas 2-(*sec*.amine)ethoxy chain containing analogs (**11b-e**) were found active at MIC 200 µM. Another analog **11a** was found inactive at MIC 200 µM. From biological activity of compounds **6** and **10** derivatives, it is evident that size of ring-C in compound **6** has detrimental role in its biological activity.

In case of 2,6-diarylpyridine derivatives, compounds (**16a-f**)[19] tested for anti-tubercular activity showed the MIC level more than 200 µM and therefore were considered to be inactive in this study.

Biological activity results of pyrazole derivatives (**19-23**) showed that 4-bromophenyl ring containing pyrazole (**19a**) had significant anti-tubercular activity at MIC value 25 µM. Other pyrazole derivatives **19e** and **19d** exhibited anti-tubercular potential at MIC values 100 and 200 µM, while **19b** and **19c** were found inactive at 200µM. The corresponding enamine analoges of pyrazoles, **20d** and **20e** showed activity at MIC values 100 and 200 µM respectively whereas, **20a-c**, **22** and **23** were found inactive at 200 µM. However, Horrocks, P. et. al. have reported MIC value 0.35 µg/mL of a pyrazole analog (**ix**, Figure 1).[16b]

In view of good anti-tubercular activity of compounds **6a**, **6c**, **8a, 19a** and **19e**, their cytoxicity was evaluated *in vitro* MTT assay using non cancerous hepatic monocytes (THP-1) cells.[17] Cytotoxicity concentration (CC_{50}) values of **6a, 6c** and **8a** was 200 µM, whereas compounds **19a**, **19e** and **20d** presented CC_{50} values more than 200 µM (Table 1).

Since, theoretically, MIC value represents IC_{100} or CC_{100} and is approximately double of the CC_{50} value. Therefore, comparing *in vitro* anti-tubercular and cytotoxicity activities of compounds **6a**, **6c**, **8a, 19a** and **19e** showed selectivity towards tubercular versus healthy cells. The most active compound **19a** was found to approximately eight times safer with respect to its MIC value.

In conclusion, we have synthesized various substituted 5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine, 1-(substituted)-4,5-dihydro-7-methoxybenzo[*g*]indazol-2-yl)ethanone, pyrazole and 2,6-diarylpyridine derivatives in good yields by an efficient methodology. Compounds **6a**, **6c**, **8a, 19a** and **19e** exhibited significant anti-tubercular activity at MIC values 50, 100, 50, 25 and 100 µM respectively in *in- vitro* assay against *Mycobacterium tuberculosis* H37Rv strain. The biological activity profile of most active derivative **19a** showed beside significant anti-tubercular activity and was found to be eight times safe with respect to its MIC value.

Overall, out of four pharmacophores studied viz **4**, **10**, **16**, **19,** pyrimidine **4** and pyrazole **19** derivatives have scope for further investigation in the quest of novel anti-tubercular agents for better treatment of MTB.

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21. a) *Representative procedure for synthesis of (E)-2-(4-hydroxybenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one* (**3**): In a 250 mL R.B. flask 6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**1**, 3 g, 17 mmol) was stirred in dioxane (20 ml) and afterward, $BF_3.Et_2O$ (0.69 ml) was added in the reaction mixture. After stirring for ten minute, 4-hydroxybenzaldehyde (**2**, 2.5 g, 8.9 mmol) was added in the reaction mixture. The reaction mixture was allowed to stir at room temperature for 72 hrs. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction, the mixture was diluted with ethyl acetate and extracted with water. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on column chromatography on silica gel using 4% ethyl acetate-hexane as eluent gave desired compound (**3**) as yellow solid; yield 71%; Rf: 0.3 (30% EtOAc in hexane); mp 172-173 ^oC; IR (KBr, νmax/cm-1): 3357 (NH_2), 3489 (OH); ^1H NMR (acetone-d_6, 300 MHz, δ ppm): 2.92 (t, 2H, *J*=6.0 Hz, CH_2), 3.11 (t, 2H, *J*=6.0 Hz, CH_2), 3.88 (s, 3H, OCH_3), 6.90 (m, 4H, Ar-H), 7.39 (d, 2H, *J*=8.4 Hz, Ar-H), 7.68 (s, 1H, CH), 7.97 (d, 1H, *J*=8.4 Hz, Ar-H), 9.35 (s, 1H, OH); ^{13}C NMR (acetone-d_6, 100 MHz, δ ppm): 27.60, 29.30, 55.58, 112.66, 113.87, 116.05 (2C), 127.50, 127.64, 130.49, 132.36 (2C), 133.54, 136.02, 146.27, 159.04, 164.03, 185.96; m/z; 281 $[M+1]^+$.

b) *Synthesis of 4-(2-amino-5,6-dihydro-8-methoxybenzo[h]quinazolin-4-yl)phenol* (**4**): In a 250 mL R.B. flask NaH (2.2 g) and DMF (7 mL) was stirred on ice bath at 0^0C for 10 minutes and subsequently, guanidine hydrochloride (3.82 gm, 40 mmol) was added. Afterward, 2-(4-hydroxybenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3**, 6 g, 21.43 mmol) dissolved in DMF (25 mL) was added in the reaction mixture and stirred for half hour at 0^0C, followed by stirring at 120 ^0C for 36 hour. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction, the mixture was diluted with ethyl acetate and extracted with water. The organic phase was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on column chromatography on silica gel using chloroform as eluent gave desired compound **4** as off-white colored solid, R_f: 0.17 (10% methanol in chloroform); mp 263-265 ^oC; IR (KBr, ν_{max}/cm^{-1}): 3357 (NH_2), 3489 (OH); ^1H NMR (DMSO-d_6, 300 MHz, δ ppm): 2.74 (bs, 2xCH_2), 3.80 (s, 3H, OCH_3), 5.74 (s, 1H, OH), 6.31 (s, 2H, NH_2), 6.83-6.92 (m, 4H, Ar-H), 7.42 (d, 2H, *J*=8.4 Hz, Ar-H), 8.09 (d, 1H, *J*=8.4 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 24.71, 28.94, 56.09, 113.38, 113.50, 113.77, 115.52 (2C), 126.86, 127.63, 129.97, 131.14 (2C), 142.19, 158.86, 160.50, 161.78, 162.81, 165.07; m/z : 320.4 $[M+1]^+$.

c) *General procedure for the synthesis of 4-(4-(2-(sec.amine)ethoxy)phenyl)-5,6-dihydro-8-methoxybenzo[h] quinazolin-2-amine* (**6**): In a 100 mL R.B. Flask, 4-(2-amino-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-4-yl)phenol (**4,** 0.2 g, 0.6 mmol) was dissolved in the mixture of acetone (40 mL) and chloroform (25 mL) at 80 ^0C. After stirring for ten minutes, anhydrous K_2CO_3 (0.4 g) and substituted amine ethylchloride hydrochloride **5** (0.13 g, 1.07 mmol) was added in reaction mixture. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction, solvent was evaporated and residue was diluted with chloroform and extracted with water. The organic phase was filtered, evaporated and dried. The crude was purified by silica gel column chromatography with a mixture of chloroform-hexane (10%) to give the desired product **6**. *4-(4-(2-(piperidin-1-yl)ethoxy)phenyl)-5,6-dihydro-8-methoxybenzo[h] quinazolin-2-amine* (**6a**): off-white colored solid; R_f: 0.23 (10% methanol in chloroform); mp 152-155 ^oC; IR (KBr, ν_{max}/cm^{-1}): 3396 (NH_2); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.26 (bs, 2H, CH_2), 1.46 (bs, 4H, 2xCH_2), 2.54 (bs, 4H, 2xNCH_2), 2.77-2.86 (bs, 6H, NCH_2 & 2xCH_2), 3.85 (s, 3H, OCH_3), 4.17 (t, 2H, OCH_2), 5.00 (s, 2H, NH_2), 6.73 (d, 1H, *J*=2.1 Hz, Ar-H), 6.86 (d, 1H, *J*=2.4 Hz, Ar-H), 6.89 (d, 2H, *J*=2.1 Hz, Ar-H), 7.50 (d, 2H, *J*=8.7 Hz, Ar-H), 8.20 (d, 1H, *J*=8.7 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 24.52, 24.73, 26.24 (2C), 29.16, 55.43 (2C), 55.72, 58.20, 66.41, 112.95, 113.24, 114.72 (2C), 115.43, 126.67, 127.83, 130.54 (2C), 131.41, 141.92, 159.79, 161.36, 161.94, 161.98, 165.04; m/z : 431.5 $[M+1]^+$.

d) *General procedure for the synthesis of ethyl (4-(2-amino-8-methoxy-5,6-dihydrobenzo[h]quinazolin-4-yl)phenoxy)alkanoate* (**8**): In a 100 mL R.B. flask, 4-(2-amino-5,6-dihydro-8-methoxybenzo[*h*]quinazolin-4-yl)phenol (**4**) (319 mg, 1 mmol) was dissolved in dimethylformamide (DMF, 9 mL) at 80 ^0C. After stirring for five minutes, anhydrous K_2CO_3 (1.1 mmol) and substituted ethyl bromoalkanoate **7** (1.5 mmol) was added in reaction mixture and stirred the reaction for 5 h. The reaction mixture was poured in cold water with vigorous stirring and neutralized it with N/5 HCl solution. The precipitate was filtered and dried. The crude was purified by column chromatography using basic alumina and a mixture of chloroform-methanol (0.5 to 1.0%) to give the desired product **8**. *Ethyl 5-(4-(2-amino-8-methoxy-5,6-dihydrobenzo[h]quinazolin-4-yl)phenoxy)pentanoate* (**8b**): off white colored solid; R_f: 0.40 (30% acetone in hexane); mp 109-110 ^oC; ^1H NMR (DMSO-d_6, 300 MHz, δ ppm): 1.19 (t, 3H, *J*=7.2 Hz, CH_3), 1.40 (bs, 4H, 2xCH_2), 2.38 (t, 2H, *J*=6.9 Hz, CH_2), 2.77 (bs, 4H, 2xCH_2), 3.82 (s, 3H, OCH_3), 4.05 (m, 4H, 2xOCH_2), 6.34 (s, 2H, NH_2), 6.86 (s, 1H, Ar-H), 6.92 (d, 1H, *J*=8.7 Hz, Ar-H), 7.01 (d, 2H, *J*=8.4 Hz, Ar-H), 7.52 (d, 2H, *J*=8.4 Hz, Ar-H), 8.11 (d, 1H, *J*=8.4 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 14.98, 22.07, 24.65, 28.86, 34.02, 35.00, 56.10, 60.59, 68.01, 113.41, 113.53, 113.85, 114.65 (2C), 126.81, 127.66, 131.08 (2C), 131.49, 142.20, 159.85, 160.59, 161.83, 162.86, 164.77, 173.65; m/z : 448.2 $[M+1]^+$.

e) *1-(3-(4-hydroxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2H-benzo[g]indazol-2-yl)ethanone* (**10**): In a 250 mL R.B. flask 8.94 mL hydrazine hydrate and of 2-(4-hydroxybenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3**, 6 g, 21.35 mmol)) in acetic acid (40 mL) were refluxed with vigorous stirring for 48 hrs. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction, reaction mixture was diluted with ethyl acetate and extracted with water. The organic phase was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on column chromatography on silica gel using chloroform as eluent gave desired compound as off-white colored solid; R_f: 0.26 (10% methanol in chloroform); mp 242-244^oC; IR (KBr, ν_{max}/cm^{-1}): 1627 (C=O), 3256 (NH_2), 3490 (OH); ^1H NMR (DMSO-d_6, 300 MHz, δ ppm): 1.83 (q, 1H, *J*=5.7 Hz, CH_2), 2.06 (q, 1H, *J*=9.6 Hz, CH), 2.20 (s, 3H, $COCH_3$), 2.82 (bs, 2H, CH_2), 3.09 (bs, 1H, CH_2), 3.75 (s, 3H, OCH_3), 4.75 (d, 1H, *J*=9.6 Hz, NCH), 6.69 (d, 2H, *J*=7.8 Hz, Ar-H), 6.79 (s, 1H, Ar-H), 6.85 (d, 1H, *J*=8.7 Hz, Ar-H), 7.03 (d, 2H, *J*=8.1 Hz, Ar-H), 7.74 (d, 1H, *J*=8.4 Hz, Ar-H), 9.35 (s, 1H, OH); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 22.99, 27.94, 29.76, 56.12 (2C), 67.10, 114.14, 114.41, 116.05 (2C), 120.56, 126.74, 127.83 (2C), 133.36, 142.69, 155.55, 157.16, 161.66; m/z : 337.1 $[M+1]^+$.

e) *General procedure for the synthesis of 1-(substituted)-4,5-dihydro-7-methoxybenzo[g]indazol-2-yl)ethanone* (**11**): In a 100 mL R.B. Flask, 1-(3,3a,4,5-tetrahydro-3-(4-hydroxyphenyl)-7-methoxybenzo[g]indazol-2-yl)ethanone (**10**, 0.2 g , 0.6 mmol) was stirred in the mixture of acetone (40 mL) and chloroform (25 mL) at 80 ^0C. After stirring for ten minutes, anhydrous K_2CO_3 (0.4 g) and substituted amine ethylchloride hydrochloride **5** (0.13 g, 1.07 mmol) was added in reaction mixture. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction, solvent was evaporated and residue was diluted with chloroform and extracted with water. The organic phase was filtered, evaporated and dried. The crude was purified by column chromatography with a mixture of chloroform-hexane (10%) to give the desired product **11**. *1-(3-(4-(1-(dimethylamino)propan-2-yloxy)phenyl)-4,5-dihydro-7-methoxybenzo[g]indazol-2-yl)ethanone* (**11d**): Off-white colored oil; R_f: 0.26 (10% methanol in chloroform); IR (neat, ν_{max}/cm^{-1}): 1626 (C=O); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 1.15 (d, 3H, *J*=6.6 Hz, CH_3), 1.59 (s, 9H, CH_2 & 2xNCH_3), 1.94 & 2.31 (m, 2H, CH_2), 2.45 (bs, 4H, CH_2), 2.87 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 4.05 (bs, 1H, OCH), 4.85 (m, 1H, CH), 6.66 (s, 1H, Ar-H), 6.80-6.86 (m, 3H, Ar-H), 7.19 (d, 2H, *J*=5.1 Hz, Ar-H), 7.88 (d, 1H, *J*=8.1 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 18.87, 22.62, 28.20, 30.05, 41.72, 46.32, 55.70, 67.24, 70.03, 109.93, 113.68, 113.96, 115.24, 116.41, 120.57, 126.87, 127.47 (2C), 134.42, 134.53, 141.68, 155.55, 158.46, 161.68, 170.62; m/z : 420.4 $[M+1]^+$.

Graphical Abstract

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Studies on substituted benzo[*h*]quinazolines, benzo[*g*]indazoles, pyrazoles, 2,6-diarylpyridines as anti-tubercular agents

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Various substituted 5,6-dihydro-8-methoxybenzo[*h*]quinazolin-2-amine, 1-(3-(4-alkoxyphenyl)-7-methoxy-3,3a,4,5-tetrahydro-2*H*-benzo[*g*] indazol-2-yl)ethanone, pyrazole and 2,6-diarylpyridine derivatives have been synthesized in good yields by an efficient methodology. The synthesized compounds (**4-23**) were evaluated for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain. Compounds **6a**, **6c**, **8a, 19a** and **19e** exhibited significant anti-tubercular activity at MIC values 50, 100, 50, 25 and 100 µM concentration. *In vitro* cytotoxicity data using THP-1 cells indicated that most active compound **19a** is safe as its MIC value is much lower than the cytotoxic value