CHAPTER FOURTEEN

Bifunctional Compounds for the Treatment of COPD

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1. INTRODUCTION

1.1. COPD pathophysiology and current therapies

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease considered to be of high unmet medical need. The disease is characterized by airflow obstruction which is only partially reversible and is often progressive in nature.[1] The pulmonary symptoms are caused by pathological changes in the lungs particularly associated with small airways disease (obstructive bronchiolitis) and emphysema (alveolar tissue destruction). In addition to a compromised lung function, the disease may also be associated with chronic cough and sputum production and systemic components such as cachexia and depression. COPD is often associated with a number of comorbidities, most notably cardiovascular disease. Long-term cigarette smoking is the most common risk factor for COPD, but exposure of the lungs to other environmental noxious particles or gases has also been

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implicated. Such exposures are believed to contribute to a chronic inflammatory process that underlies the disease progression in predisposed individuals. Chronic inflammatory processes lead to structural remodeling including narrowing of the small airways and parenchymal destruction and loss of lung elastic recoil which causes the loss of lung function.[1] COPD is of increasing concern as a major public health problem with increasing rates of morbidity and mortality. It is projected to be the fourth major burden of disease and the third leading cause of death by 2030.[2,3]

Inhaled bronchodilators are central to symptomatic relief in COPD and two major classes exist: β_2-adrenoceptor agonists (beta agonists) and anticholinergics (Fig. 14.1). Beta agonists act on β_2 receptors, which are seven-transmembrane domain-spanning G-protein-coupled receptors (GPCRs) situated on the

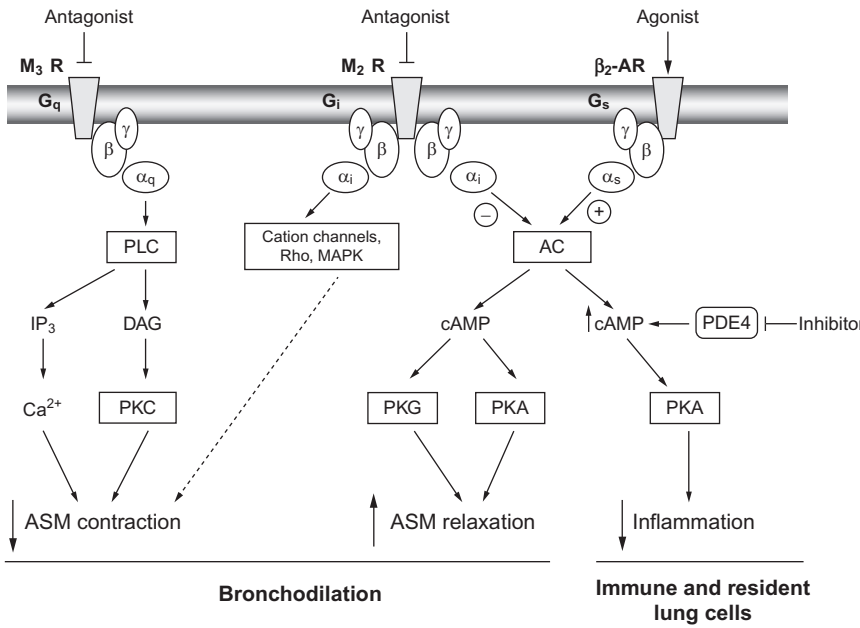


Figure 14.1 Interaction of muscarinic M_2 and M_3 receptor- and β_2-adrenoceptor-mediated intracellular signaling pathways and their modulation by muscarinic antagonists, β_2 agonists, and PDE4 inhibitors to elicit bronchodilation and anti-inflammatory activity in the lungs. (Adapted with kind permission from Springer Science+Business Media from Ref. 4.) Abbreviations: M_2, muscarinic 2 receptor; M_3, muscarinic 3 receptor; β_2, β_2 adrenoceptor; G_q, G_i, G_s: G proteins; α: alpha, β: beta, γ: gamma, G-protein subunits; PLC, phospholipase C; IP3, inositol 1,4,5-triphosphate; DAG, sn-1,2-diacylglycerol; Ca^{2+}, calcium ions; PKC, protein kinase C; AC, adenylyl cyclase; cAMP, cyclic adenosine 3′,5′ monophosphate; PKG, protein kinase G; PKA, protein kinase A; ASM, airway smooth muscle; PDE4, phosphodiesterase-4; −, negative regulator of cAMP; +, positive regulator of cAMP; Rho, rho-associated kinases; MAPK, mitogen-activated protein kinases.

smooth muscle cells in the airways. There are three subtypes of β adrenoceptors (β_1–β_3) which mediate the actions of adrenaline and noradrenaline. β_1 Receptors are present in the heart, and agonist binding can elicit both increases in heart rate and force of contraction. Functional selectivity of agonists for β_2 over β_1 receptors is therefore desirable as it could increase the therapeutic index for β_2-mediated bronchodilation over unwanted β_1-mediated increases in heart rate. β_2 Receptors are coupled to G_s proteins which activate adenylyl cyclase leading to formation of cyclic AMP. This elevation of intracellular cyclic AMP leads to relaxation of the smooth muscle and bronchodilation.[5] Muscarinic receptors are seven-transmembrane-spanning GPCRs which mediate acetylcholine (ACh) signaling from the cell surface. There are a total of five muscarinic receptor subtypes (M_1–M_5) of which M_1, M_2, and M_3 are present in the lungs. M_1 and M_3 receptors are coupled to G_q proteins and utilize calcium as a second messenger through the action of phospholipase C and inositol triphosphate, whereas M_2 receptors are G_i linked which decreases cellular cyclic AMP levels and inhibits voltage-gated calcium channels.[6] Muscarinic receptor antagonists act to block ACh signaling, thereby inhibiting the airway smooth muscle contraction which leads to bronchoconstriction. Muscarinic M_1 receptors are located on parasympathetic nerve ganglia and are responsible for facilitation of nerve transmission. M_2 receptors are located on postganglionic parasympathetic nerves and are the predominant receptor subtype on airway smooth muscle. The function of M_2 receptors is autoinhibitory which serves to maintain a tight regulation of ACh release. Muscarinic M_3 receptors are also located on airway smooth muscle cells and mediate airway smooth muscle contraction. Blockade of both M_1 and M_3 muscarinic receptor subtypes inhibits cholinergic-mediated bronchoconstriction. Presently, long-acting β_2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) are used as the standard of care for symptomatic control in COPD.[7]

Recently, roflumilast, a novel oral anti-inflammatory agent that inhibits phosphodiesterase 4 (PDE4) enzyme activity, was approved for treatment of moderate and severe COPD associated with chronic bronchitis in patients at risk of exacerbations.[8] While the clinical effect of roflumilast and related PDE4 inhibitors are as anti-inflammatory agents rather than as bronchodilators, PDE4 is present in airway smooth muscle cells and is responsible for the hydrolysis of cyclic AMP, which is important in bronchodilation. This compound has been shown to be effective in improving lung function as an add-on to the LABA, salmeterol and the LAMA, tiotropium bromide.[9] To date, to the authors' knowledge, no inhaled PDE4 inhibitors have progressed to registration trials in pulmonary disease. The pursuit of PDE4 subtype selective inhibitors has also been an area of high pharmaceutical

industry interest as a way to achieve clinical efficacy and improve the systemic adverse effects associated with the compound drug class.[10] There is also emerging preclinical evidence that dual PDE3/PDE4 inhibitors can combine bronchodilatory effects via direct PDE3 inhibition and act as an anti-inflammatory, which could be an alternative novel therapeutic approach.[11]

Inhaled glucocorticoids have a broad range of anti-inflammatory actions through binding and activating cytosolic glucocorticoid receptor (GR)-α. Upon glucocorticoid binding with GR-α, the complex formed translocates to the cellular nucleus where it can bind with a glucocorticoid response element in the promoter region of target genes to modulate gene expression. Glucocorticoids can mediate both gene repression (transrepression) and gene induction (transactivation) to exert their anti-inflammatory effects.[12] The level of efficacy achieved by inhaled glucocorticoids in COPD remains a controversial topic but they do improve symptoms, lung function, and reduce exacerbations in more severe patients.[1] The combination of an inhaled β_2 agonist and glucocorticoid therapies has been shown to be superior to individual treatments alone with respect to lung function and health status as well as reducing disease-related exacerbations in patients with moderate to severe disease.[13]

1.2. Bifunctional compounds: Concepts and advantages

Combination products consisting of two medications and two modes of action have been highly successful. Seretide®/Advair®, a combination of the LABA, salmeterol, and the inhaled corticosteroid, fluticasone propionate, used for both COPD and asthma, was the prescription drug with the third highest sales in 2010.[14] Coadministration of two mechanistically distinct chemical entities is one approach for combination drug therapy, but it is also possible to use a "bifunctional compound," also referred as a "dual selective pharmacology molecule," which is a single chemical entity with two distinct pharmacophores covalently bonded. While the design seems conceptually simple, connection points and linkers must be chosen carefully, as the choices can significantly impact the activity of either pharmacophore. The compounds, being the combination of two pharmacophores, tend to have high molecular weights, but the net molecular size may offer an advantage as an inhaled therapeutic, because it can result in greater lung retention and lower oral bioavailability, thereby reducing systemic exposure and related downstream toxicology issues.[15] Due to the size of the molecules and the inherent flexibility of many of the linkers, it

may also be a challenge to obtain crystalline compounds for development. However, a single chemical entity with two activities would offer multiple advantages, including matched pharmacokinetics, simplified formulation, and simplified clinical development.[16] Significantly, there is potential for a combination product consisting of a novel bifunctional compound and a separate additional medication in a single device to deliver three mechanisms. The alternative development and engineering of an inhaler capable of delivering these separate drugs, with unique disease-related mechanisms, is yet to be realized.

Described herein are novel bifunctional molecules designed through linking of pharmacophores of approved therapeutic targets: muscarinic antagonists, β agonists, and PDE4 inhibitors. Additional combination examples, such as neutrophil elastase inhibitor/muscarinic antagonist[17] or epithelial sodium channel inhibitor/β agonist,[18] have also been disclosed.

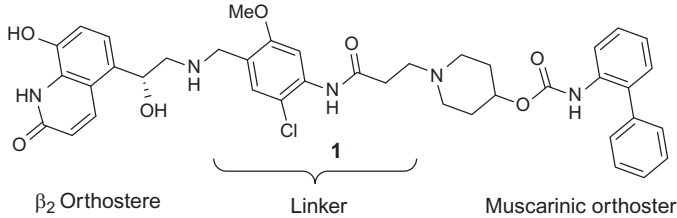
2. BIFUNCTIONAL STRATEGIES AND COMPOUNDS

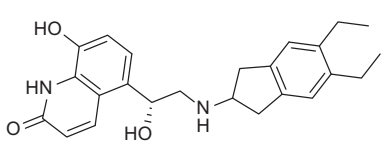
2.1. Muscarinic receptor antagonist–β_2 agonist

Clinical trials have demonstrated that the combination of an individually dosed muscarinic antagonist along with a β agonist provides greater bronchodilation than either component alone.[19] The two mechanisms are complementary, with the β_2 agonist increasing cyclic AMP, leading to smooth muscle relaxation, while the muscarinic antagonist blocks ACh-mediated bronchoconstriction. Furthermore, the addition of a β_2 agonist actually decreases the amount of ACh released, thereby amplifying the effect induced by the muscarinic antagonist. Combivent®, an inhaled combination product used for the relief of symptoms, contains the short-acting β agonist, albuterol, and the short-acting muscarinic antagonist, ipratropium. Combining long-acting agents with each individual mechanism is recommended therapy for more severe COPD,[1] yet no single commercial inhalation device is currently marketed which delivers both therapeutics, although clinical trials are underway.[20]

Bifunctional compounds comprised of pharmacophores representing each class of bronchodilators have been reviewed.[20] One such compound (GSK961081, TD5959, structure not disclosed) has been reported to be in clinical studies both as a stand-alone drug and in combination with fluticasone propionate, an inhaled corticosteroid.[21] The structure of GSK961081 has been speculated to be **1**, as developable salts of this compound have been reported.[22–25] Compound **1** connects the common quinolinone head

group of indacaterol (**2**) with the biphenyl of the muscarinic receptor antagonist, YM-46303 (**3**).[26] Once-daily administration of GSK961081 has shown equivalent changes in FEV_1 to once-daily tiotropium (LAMA) plus twice-daily salmeterol (LABA) after 14 days in COPD patients.[16]





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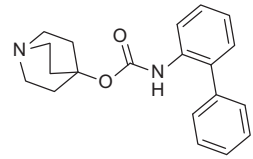

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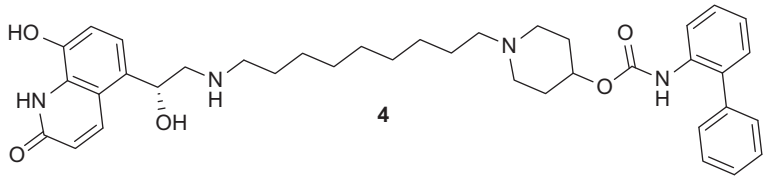
A detailed characterization of a related compound with the same key pharmacophores, THRX-198321 (**4**) has been reported.[22,27–29] Compound **4** is reported to have a K_i for the β_2 receptor of 3.5 nM and for the M_3 receptor of 0.01 nM with greater than eightfold selectivity for β_2 over β_1.[22,30] A systematic study of chain length resulted in the identification of the nine-carbon spacer between the two pharmacophores as being optimal for highest activity on both receptors. Representative β_2-active moieties were also compared, with the quinolinone moiety providing the most potent β_2-agonist activity and concomitant potentiation of M_3 antagonist activity. Increased binding affinity at each receptor was reported for **4** over the respective fragments, which was proposed to be due to simultaneous binding of the alternate pharmacophore to an allosteric binding site in each protein.[27]



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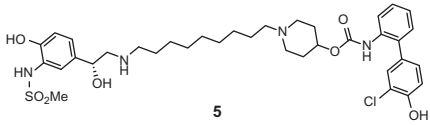
The biaryl moiety is often utilized as a muscarinic bioactive fragment.[31–37] Compound **5** is described to have an EC_{50} as a β_2 agonist of 0.13 nM and an IC_{50} on the M_3 receptor of 0.72 nM.[31] A similar series with the same pharmacophores separated by a diamide linker has also been disclosed.[32]

A similar compound, **6** is reported to have a K_i of less than 30 nM against the β_2 receptor with greater than 10-fold β_2/β_1 selectivity and a K_i of less than 10 nM against the M_3.[33] A related patent application discloses various alternatives to the distal aryl group of the biphenyl, including thiophene, thiazole, and pyridine, with the thiophene **7** having activity against both receptors less than 10 nM (K_i) and greater than fivefold selectivity for β_2 over β_1.[34] Another application describes an acyclic linker replacement for the piperidine, with the activity of **8** being less than 300 nM against M_3 and β_2 receptors.[35] Compounds similar to **1** with a substituted phenyl in the linker and a formoterol-like β_2-agonist head group as exemplified by **9**, exhibit activity against both receptors less than 10 nM (K_i) and greater than 100-fold selectivity for β_2 over β_3 and β_1 subtypes.[36,37]



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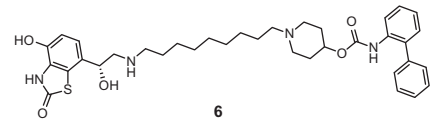

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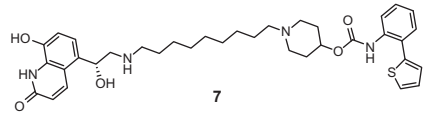

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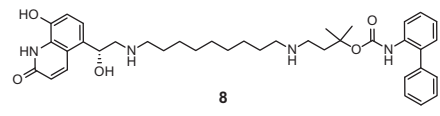

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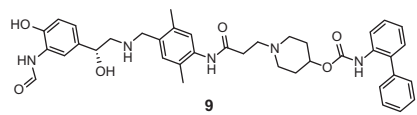

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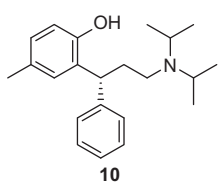
Conjugation of the muscarinic antagonist tolterodine (**10**) to β_2 agonists have resulted in the discovery of new muscarinic receptor antagonist–β_2 agonists (MABAs) such as **11** (M_3 K_i 0.3 nM, β_2 EC_{50} 2.4 nM).[38] Various examples with common β_2 moieties and tethers were compared, with most compounds showing good potency against both targets, with the quinolinone-containing fragment being the most potent. The compounds, being optimized for inhaled delivery, were designed to have poor oral availability and low metabolic stability to minimize systemic exposure. A patent application covering MABAs with the headpiece containing **10** has appeared.[39]



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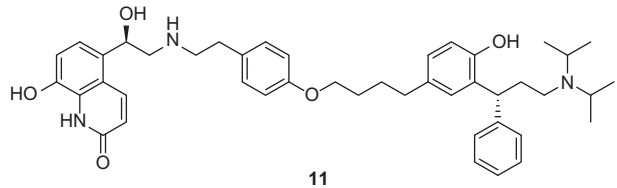

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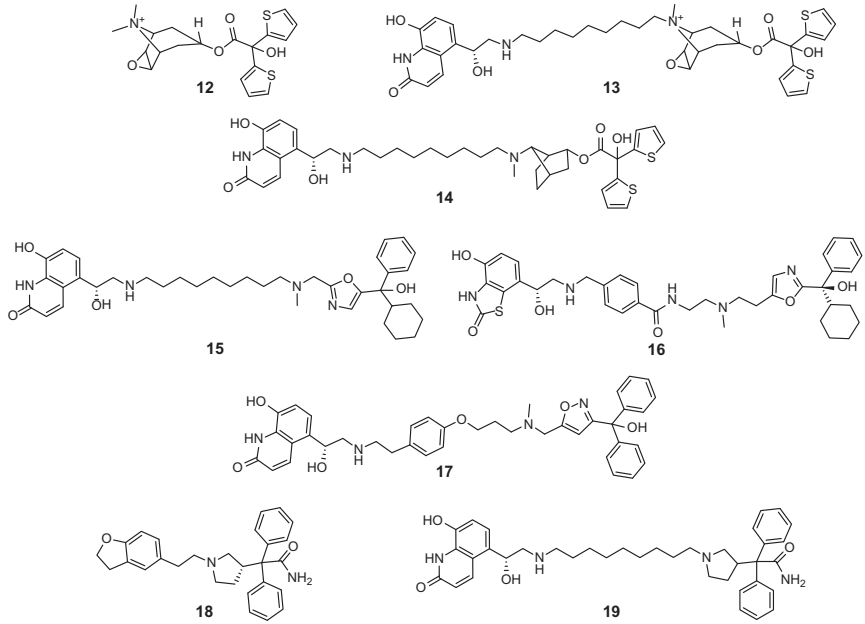
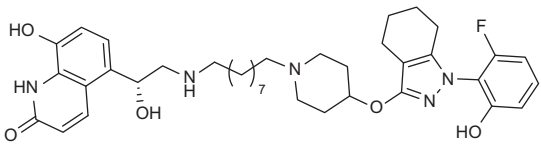
Another often appearing muscarinic receptor antagonist moiety utilized in bifunctional compound design is based on the biarylmethylene of tiotropium bromide (**12**). Linking to a quinolinone provided **13** (K_i under 50 nM against β_2 and M_3 receptors).[40] Related compounds have been described with the tertiary amine (**14**) reported to be less than 100 nM against the β_2 receptor and less than 1 nM on the M_3 receptor.[41] The naphthalene-1,5-disulfonate salt of **14** has also been described as well as additional related compounds.[42–45] The bicyclic moieties have been replaced with an oxazole to give **15** with a K_i less than 100 nM against the β_2 receptor and less than 5 μM against the M_3 receptor.[46] Additional five-membered ring heterocycles in the linker have also been exemplified with **16** having an IC_{50} of 4 nM on M_3 binding and an EC_{50} of 1.2 nM[47] and **17** having an IC_{50} of 0.1 nM on M_3 binding and an EC_{50} of 2 nM.[48] Related triazoles have also been reported.[49] Further work around the biarylmethylenes, including quaternary amines in the linker, has been described.[50] The alcohol has been replaced with a carboxamide as in darifenacin, **18**,[51] to give **19** with a K_i less than 50 nM against both receptors.[52]



Additional examples with unique muscarinic pharmacophores have also been reported.[53–55] One such example (**20**) began with a novel, selective M_3 antagonist (**21**) which evolved from a nonselective norepinephrine reuptake inhibitor.[56] Compound **20** has high clearance in microsomes and poor membrane permeability, a favorable profile for an inhaled therapeutic.



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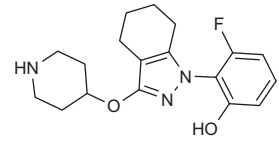

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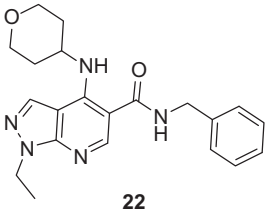
2.2. Muscarinic receptor antagonist–PDE4 inhibitor

Addition of an oral PDE4 inhibitor with an inhaled muscarinic receptor antagonist has clinical benefit in improving lung function in COPD beyond the effect of muscarinic antagonist treatment alone.[57] An inhaled bifunctional molecule against both these targets, therefore, has the potential for improved efficacy as the systemic side effects, which are dose limiting to oral PDE4 inhibitors, are less likely to be of concern. Additionally, a PDE4 inhibitor and antimuscarinic bifunctional molecule could be codosed with either a β_2 agonist or glucocorticoid to target two bronchodilator or anti-inflammatory mechanisms. More conventional small molecules with such dual activity have been identified.[58,59]

A series of four related applications have appeared that describe bifunctional compounds in which a PDE4 inhibitor is connected to a muscarinic receptor antagonist.[60–63] All utilize a pyrazolopyridine (**22**)[64] as the PDE4 inhibitor and a biaryl-containing muscarinic antagonist, but differ in the linker. A muscarinic receptor antagonist such as **23**[65] used in **24**, with only a urea separating the pharmacophores, is reported to be active against both targets, although the specific activities are not reported.[63] Bifunctional compounds of this class tend to have shorter linkers, suggesting that the activity of each pharmacophore is less sensitive to the presence of the other.



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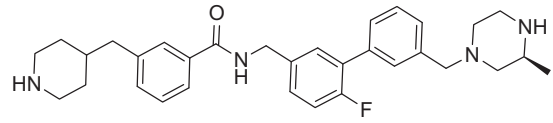

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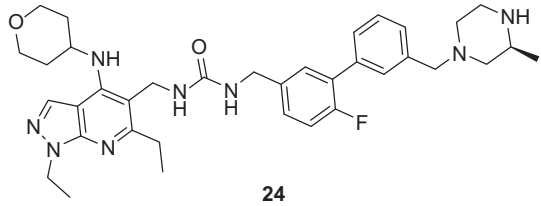

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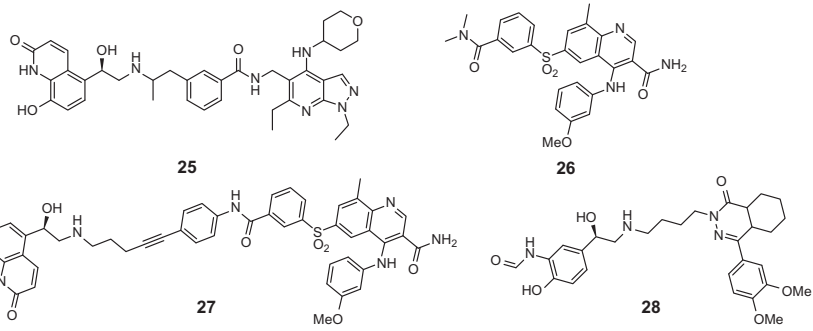
2.3. PDE4 inhibitor–β_2 agonist

Conceptually, the conjugation of a β_2 agonist to a PDE4 inhibitor could be an alternative way for developing a single molecule with both bronchodilator and anti-inflammatory properties. In support of this approach, the addition of the oral PDE4 inhibitor roflumilast to an inhaled β_2 agonist has demonstrated clinical efficacy for improved lung function over β_2-agonist treatment alone.[57] A potential advantage of this combination is that both β_2 agonists and PDE4 inhibitors rely on modulation of the secondary messenger cyclic AMP to elicit their effects, and it is possible that the combination could provide additive or synergistic pulmonary anti-inflammatory activity. Studies reporting positive anti-inflammatory interactions through modulation of cyclic AMP using a combination of β_2 agonist and PDE4 inhibitor have been reported in human immune cells and lung fibroblasts.[66,67]

Three applications have appeared which describe the combination of a PDE4 inhibitor with a β_2 agonist.[37,68,69] The applications differentiate from one another by the PDE4 inhibitor pharmacophore that is utilized. In one, the standard set of β_2-agonist head groups is connected with a pyrazolopyridine PDE4 inhibitor (**22**) to give compounds exemplified by **25** (IC_{50}s against both targets are less than 100 nM).[68] Another example connects GSK256066 (**26**)[70] with a variety of similar linkers and a standard set of β_2-agonist head groups of which **27** is an example (IC_{50} against both targets less than 100 nM).[69] Another study describes the connection shown in **28**, which has an EC_{50} of 0.1 nM for relaxation of guinea pig tracheal smooth muscle in an *ex vivo* assay and an IC_{50} of 260 nM as a PDE4 inhibitor.[71] The authors describe the β_2-agonist activity to be sensitive to chain length, with little effect on PDE4 activity.



3. CONCLUSIONS

There remains great need for the discovery and development of more efficacious and novel treatments for COPD. The development of bifunctional molecules may be ideally suited toward inhaled delivery, given their physical chemical properties, which should favor lung retention while minimizing systemic adverse effects and toxicity. In the absence of more sophisticated delivery devices that could deliver multiple combinations, the utilization of bifunctional compounds has been predicted to be a potential future basis of a therapeutic regimen that affects three targets and which would consist of the combination of a bifunctional compound with another agent.[16] It is also tempting to speculate that in the future, a quadruple target treatment may also be possible based on a combination of two bifunctional molecules delivered in currently available oral inhalation devices.

REFERENCES

(1) Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of COPD. Revised 2011. Available from http//www.goldcopd.org/uploads/users/files/GOLD_Report_2011Feb21.pdf.
(2) Mathers, C.C.; Loncar, D. *PLoS Med.* **2006**, *3*, e442.
(3) Chapman, K.R.; Mannino, D.M.; Soriano, J.B.; Vermeire, P.A.; Buist1, A.S.; Thune, M.J.; Connelle, C.; Jemale, A.; Lee, T.A.; Miravitlles, M.; Aldington, S.; Beasley, R. *Eur. Respir. J.* **2006**, *27*, 188.
(4) Meurs, H.; Roffel, A.F.; Elzinga, C.R.; Zaagsma, J. In *Muscarinic Receptors in Airways Disease*; Zaagsma, J., Meurs, H., Roffel, A.F., Eds.; Birkhauser-Verlag: Basel, 2001; pp 121–157.
(5) Johnson, M. *J. Allergy Clin. Immunol.* **2006**, *117*, 18.
(6) Gosens, R.; Zaagsma, J.; Meurs, H.; Halayko, A.J. *Respir. Res.* **2006**, 7, 73.
(7) Lainé, D.I. *Expert Rev. Clin. Pharmacol.* **2010**, *3*, 43.
(8) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM207377.pdf.
(9) Gross, N.J.; Giembycz, M.A.; Rennard, S.I. *COPD* **2010**, 7, 141.
(10) Page, C.P.; Spina, D. *Curr. Opin. Pharmacol.* **2012**, *12*, 1.
(11) Boswell-Smith, V.; Cazzola, M.; Page, C.P. *J. Allergy Clin. Immunol.* **2006**, *117*, 1237.
(12) Newton, R.; Holden, N. *Mol. Pharmacol.* **2007**, *72*, 799.
(13) Calverley, P.M.; Anderson, J.A.; Celli, B.; Ferguson, G.T.; Jenkins, C.; Jones, P.W.; Yates, J.C.; Vestbo, J. *N. Engl. J. Med.* **2007**, *356*, 775.
(14) Arrowsmith, J. *Nat. Rev. Drug Dis.* **2012**, *11*, 17.
(15) Robinson, C.; Zhang, J.; Garrod, D.R.; Newton, G.K.; Jenkins, K.; Perrior, T.R. *Future Med. Chem.* **2011**, *3*, 1567.
(16) Matera, M.G.; Page, C.P.; Cazzola, M. *Trends Pharm. Sci.* **2011**, *32*, 495.
(17) Finch, H.; Ray, N. C.; Edwards, C. Patent Application WO 060203, **2009**.
(18) Johnson, M. R.; Hirsch, A. J.; Boucher, R. C.; Zhang, J. Patent Application WO 146869, **2007**.

(19) Cazzola, M.; Molimard, M. *Pulm. Pharmacol. Ther.* **2010**, *23*, 257.
(20) Hughes, A.D.; Jones, L.H. *Future Med. Chem.* **2011**, *3*, 1585.
(21) Theravance. Press Release October 27, **2011**. www.theravance.com.
(22) Mammen, M.; Dunham, S.; Hughes, A.; Lee, T. W.; Husfeld, C.; Stangeland, E. Patent Application WO 074246, **2004**.
(23) Ray, N.C.; Alcaraz, L. *Expert Opin.* **2009**, *19*, 1.
(24) Chudasama, R.; Kennedy, A.; Kindon, L. J.; Mallet, F. P. Patent Application WO 090859, **2007**.
(25) Chao, R. S.; Rapta, M.; Colson, P. Patent Application WO 023454, **2006**.
(26) Naito, R.; Takeuchi, M.; Morihira, K.; Hayakawa, M.; Ikeda, K.; Shibanuma, T.; Isomura, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1286.
(27) Steinfeld, T.; Hughes, A.D.; Klein, U.; Smith, J.A.M.; Mammen, M. *Mol. Pharmacol.* **2011**, *79*, 389.
(28) Mammen, M.; Dunham, S.; Hughes, A. Patent Application WO 074812, **2004**.
(29) Mammen, M.; Dunham, S.; Hughes, A.; Lee, T. W. Patent Application WO 074276, **2004**.
(30) Hughes, A.D.; Chin, K.H.; Dunham, S.L.; Jasper, J.R.; King, K.E.; Lee, T.W.; Mammen, M.; Martin, J.; Steinfeld, T. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1354.
(31) Jones, L. H.; Lunn, G.; Price, D. A. Patent Application WO 041095, **2008**.
(32) Hughes, A.; Byun, D.; Chen, Y.; Fleury, M.; Jacobsen, J. R.; Strangeland, E. R.; Wilson, R. D.; Yen, R. Patent Application WO 123766, **2010**.
(33) Mammen, M.; Dunham, S. Patent Application WO 051946, **2005**.
(34) Mammen, M.; Mischki, T.; Hughes, A.; Ji, Y. Patent Application WO 023460, **2006**.
(35) Mammen, M.; Mischki, T. Patent Application WO 023457, **2006**.
(36) Colson, P.; Hughes, A.; Husfeld, C.; Mammen, M.; Rapta, M. Patent Application WO 127196, **2007**.
(37) Collingwood, S. P.; Fairhurst, R. A.; Press, N. J. Patent Application WO 000483, **2008**.
(38) Jones, L.H.; Baldock, H.; Bunnage, M.E.; Burrows, J.; Clarke, N.; Coghlan, M.; Entwistle, D.; Fairman, D.; Feeder, N.; Fulton, C.; Hilton, L.; James, K.; Jones, R.M.; Kenyon, A.S.; Marshal, S.; Newman, S.D.; Osborne, R.A.; Patel, S.; Selby, M.D.; Stuart, E.F.; Trevethick, M.A.; Wright, K.N.; Price, D.A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2759.
(39) James, K.; Jones, L. H.; Price, D. A. Patent Application WO 107828, **2007**.
(40) Mammen, M.; Hughes, A. Patent Application WO 106333, **2004**.
(41) Finch, H.; Ray, N. C.; Bull, R. J.; Neil, M. B.; Jennings, A. S. R. Patent Application WO 017670, **2007**.
(42) Finch, H.; Bull, R. J. Patent Application WO 017824, **2008**.
(43) Alcaraz, L.; Kindon, N.; Sutton, J. Patent Application WO 096127, **2008**.
(44) Alcaraz, L.; Kindon, N.; Sutton, J. Patent Application WO 149110, **2008**.
(45) Bourssou, T.; Schnapp, A.; Lustenberger, P.; Rudolf, K.; Pieper, M. P.; Grauert, M.; Breitfelder, S.; Speck, G. Patent Application WO 111004, **2005**.
(46) Ray, N. C.; Bull, R. J.; Finch, H.; Van Den Heuvel, M.; Bravo, J. A. Patent Application WO 017669, **2008**.
(47) Edwards, C.; Kindon, N.; Ray, N. C.; Sutton, J. M.; Alcaraz, L. Patent Application WO 006129, **2009**.
(48) Sutton, J. M.; Roussel, F.; Van Den Heuvel, M.; Ray, N. C.; Alcaraz, L. Patent Application WO 015792, **2010**.
(49) Jones, L. H.; Roberts, D. F.; Strang, R. S. Patent Application WO 004517, **2010**.
(50) Finch, H.; Bull, R. J.; Sutton, J. M. Patent Application WO 017827, **2008**.
(51) Haab, F. *Drugs Today* **2005**, *41*, 441.
(52) Mammen, M.; Hughes, A. Patent Application WO 089892, **2004**.

(53) Jennings, A. S. R.; Ray, N. C.; Roussel, F.; Sutton, J. M. Patent Application WO 154678, **2011**.
(54) Alcaraz, L.; Bailey, A.; Bull, R. J.; Johnson, T.; Kindon, N. D.; Lister, A. S.; Robbins, A. J.; Stocks, M. J.; Tobald, B. Patent Application WO 008448, **2009**.
(55) Alcaraz, L.; Bailey, A.; Kindon, N. Patent Application WO 012896, **2011**.
(56) Osborne, R.; Clark, N.; Glossop, P.; Kenyon, A.; Liu, H.; Patel, S.; Summerhill, S.; Jones, L.H. *J. Med. Chem.* **2011**, *54*, 6998.
(57) Fabbri, L.M.; Calverley, P.M.; Izquierdo-Alonso, J.L.; Bundschuh, D.S.; Brose, M.; Martinez, F.J.; Rabe, K.F. *Lancet* **2009**, *374*, 695.
(58) Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Durieu, V.; Gillard, M.; Lebon, F.; Lengele, S.; Que´re, L.; van Keulen, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1834.
(59) Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Gillard, M.; Que´re´, L.; Stebbins, K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3077.
(60) Callahan, J. F.; Lin, G.; Wan, Z.; Yan, H. Patent Application WO 100166, **2009**.
(61) Callahan, J. F.; Lin, G.; Wan, Z.; Yan, H. Patent Application WO 100167, **2009**.
(62) Callahan, J. F.; Li, T.; Wan, Z.; Yan, H. Patent Application WO 100169, **2009**.
(63) Callahan, J. F.; Wan, Z.; Yan, H. Patent Application WO 100170, **2009**.
(64) Hamblin, J.N.; Angell, T.D.R.; Ballantine, S.P.; Cook, C.M.; Cooper, A.W.J.; Dawson, J.; Delves, C.J.; Jones, P.S.; Lindvall, M.; Lucas, F.S.; Mitchell, C.J.; Neu, M.Y.; Ranshaw, L.E.; Solanke, Y.E.; Somers, D.O.; Wiseman, J.O. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4237.
(65) Jin, J.; Budzik, B.; Wang, Y.; Shi, D.; Wang, F.; Xie, H.; Wan, Z.; Zhu, C.; Foley, J.J.; Webb, E.F.; Berlanga, M.; Burman, M.; Sarau, H.M.; Morrow, D.M.; Moore, M.L.; Rivero, R.A.; Palovich, M.; Salmon, M.; Belmonte, K.E.; Laine, D.I. *J. Med. Chem.* **2008**, *51*, 5915.
(66) Tannheimer, S.L.; Sorensen, E.A.; Haran, A.C.; Mansfield, C.N.; Wright, C.D.; Salmon, M. *Pulm. Pharmacol. Ther.* **2012**, *25*, 178.
(67) Tannheimer, S.L.; Wright, C.D.; Salmon, M. *Respir. Res.* **2012**, *13*, 28.
(68) Baker, W. R.; Cai, S.; Kaplan, J. A.; Kim, M.; Phillips, G.; Purvis, L.; Stasiak, M.; Stevens, K. L.; Van Veldhuizen, J. Patent Application WO 143106, **2011**.
(69) Baker, W. R.; Cai, S.; Kaplan, J. A.; Kim, M.; Loyer-Drew, J. A.; Perrault, S.; Phillips, G.; Purvis, L.; Stasiak, M.; Stevens, K. L.; Van Veldhuizen, J. Patent Application WO 143105, **2011**.
(70) Tralau-Stewart, C.J.; Williamson, R.A.; Nials, A.T.; Gascoigne, M.; Dawson, J.; Hart, G.J.; Angell, A.D.R.; Solanke, Y.E.; Lucas, F.S.; Wiseman, J.; Ward, P.; Ranshaw, L.E.; Knowles, R.G. *J. Pharmacol. Exp. Ther.* **2011**, *337*, 145.
(71) Shan, W.; Huang, L.; Zhou, Q.; Jiang, H.; Luo, Z.; Lai, K.; Li, X. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1523.